FUNCTIONAL PATHOLOGY OF INTERNAL DISEASES

BY

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WITH ONE HUNDRED AND THIRTY-EIGHT ILLUSTRATIONS IN TEXT

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Preface

The study of disease from the functional standpoint has progressed rapidly in recent years. Advances in physiology, biochemistry, immunology and experimental pathology, as well as the careful and systematic study of patients, have thrown much new light upon disturbances of function. To the physician these advances have been of increasing significance. Not only have they served to interpret the clinical pictures with which he comes in contact, but they have pointed the way to new diagnostic methods and have furnished new indications for treatment.

The present book deals with those changes in function that are presented by patients suffering from internal diseases. The rapid progress in this field and the fact that it has been attacked from so many points of view make its presentation by a single individual one of peculiar difficulty. It is to be hoped, however, that a selection and discussion of topics by one whose primary interest lies in the clinic will prove of value to those who are also dealing with patients.

In order to make the presentation more brief and more readable, historical and controversial matter has in general been omitted and the author has often expressed an arbitrary opinion on still debatable subjects. For more complete discussions the reader is referred to the larger monographs and reviews cited at the end of each chapter. In these, summarized accounts of the earlier literature will be found. Additional references, mainly to recent literature, have also been cited, and for the benefit of those who do not read foreign languages preference has been given to articles that have appeared in English.

A. W. Hewlett.

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FUNCTIONAL PATHOLOGY

Chapter I

The Circulation

The blood acts as a transporting medium for the body. In it oxygen is carried from the lungs to the tissues and carbon dioxid is carried from the tissues to the lungs. Nutrient materials, absorbed from the gastro-intestinal tract, are delivered to various parts of the body for use or for storage, and waste products are carried from the tissues to the excretory organs. Not only does the blood act as a carrying medium for supplies and wastes, but it also serves as a means of communication between different parts of the body; for substances that enter the blood from one organ may exert a controlling influence upon the physiological activities of other parts of the body.

Cardiovascular System.—In order to perform these functions the blood must be kept in constant circulation through the various organs and tissues. This is accomplished by the cardiovascular system, the heart and the blood vessels. The *left ventricle* receives blood from the lungs and pumps it into the aorta. The great arteries that branch off from the aorta act as a distributing system for the different parts of the body. The finer branches in which these arteries terminate, i. e., the arterioles and capillaries, oppose a considerable resistance to the flow of blood by reason of their small caliber. For this reason blood is held back in the aorta and larger arteries under an increased pressure. This high arterial pressure makes it possible to furnish blood to the upper portions of the body and particularly to the brain. Furthermore, when an increased supply of blood is required in any particular organ, the vessels leading to this organ can be opened more widely than usual, so that the blood flows through that region with increased speed; just as the opening of a tap in a city water system causes an increased flow of water to that particular part of the system. Owing to the resistance offered to the flow of blood in the arterioles and capillaries, the pressure falls rapidly in these vessels and the pressure in the veins that enter the thorax is but little above the atmospheric pressure.

The *right ventricle* receives blood from the large veins of the body and pumps it through the pulmonary circuit, where it undergoes alterations in its content of oxygen and of carbon dioxid. In the lungs the capillaries are short and offer relatively little resistance to the flow of

blood through them. For this reason the pressure in the pulmonary artery is only about one-third that in the aorta. Furthermore, as all portions of the lungs possess the same function there is no need for variations in the distribution of blood to different parts of the pulmonary area, and so far as we know such variations do not occur under physiological conditions.

Ventricular Outputs.—The amounts of blood pumped out by the two sides of the heart must in the long run be equal to each other. Were this not so, all of the blood would tend to accumulate either in the pulmonary or in the systemic vessels. Such a condition is obviously incompatible with life. Under physiological conditions slight variations undoubtedly occur in the distribution of blood between the pulmonary and systemic circuits, and under pathological conditions these variations may be increased; but in all cases a stationary condition is soon reached in which each side of the heart again pumps out equal amounts of blood. When we consider the numerous physiological and pathological variations in the circulation, both as regards blood pressure and rate of blood flow, it is evident that some physiological adjustment must control the activities of the two sides of the heart, so that in the long run the output from the one shall always equal the output from the other.

The Heart

Dynamics of the Heart Muscle

The heart muscle is obviously capable of adjusting its contractions to varying conditions, both as regards the quantity of blood that is to be pumped and the arterial pressure against which this pumping must be done. The laws governing its contractions appear to be very similar to those which govern the response of an isolated voluntary muscle, such as the frog's gastrocnemius, when the latter is stimulated by a single electric shock applied to its nerve. Since the manner in which the heart adapts itself to different demands is relatively difficult to study, it seems advisable to consider, first, the factors that govern the contractions of an isolated voluntary muscle, and, then, to compare these with the factors that govern the heart muscle itself.

Isometric and Isotonic Contractions

Two types of muscular contraction must be distinguished. In the *first*, or *isometric contraction*, the ends of the muscle are fixed and no shortening can take place. The state of contraction expresses itself by an increased tension in the muscle. In the *second*, or *isotonic type of*

contraction, the tension of the muscle remains constant throughout and the state of contraction expresses itself by a shortening. In either case the contraction is accompanied by a more active metabolism in the muscle and an increased liberation of heat.

Elasticity and Tension.—In considering the behavior of the contracting muscle it is of great assistance to adopt the conception of Weber, that the condition of contraction involves a change in the elastic properties of the muscle. During its relaxed state the muscle can be stretched, within physiological limits, by a relatively light load. During its contracted state, on the other hand, the muscle can be stretched only by relatively heavy loads. If the length be fixed, the change in elasticity during contraction increases the tension. If the tension be fixed, the change in elasticity shortens the muscle. Furthermore, there exists a definite relation between the length of the muscle and its tension in both the relaxed and the contracted state. This relation can be determined by causing the muscle to contract isometrically after it has been stretched to different initial lengths. The curves plotted from such a series of measurements are shown in Figure 1. It will be seen that when the muscle is relaxed, it may be stretched to and beyond its physiological length with but a slight increase of tension. When it is contracted, on the other hand, a considerable increase of tension accompanies each increase in length. The change in tension which occurs during any isometric contraction of the muscle is represented on this diagram by the horizontal distance between the two curves. It is evident that this change increases with each increase in the initial length of the muscle, up to and somewhat

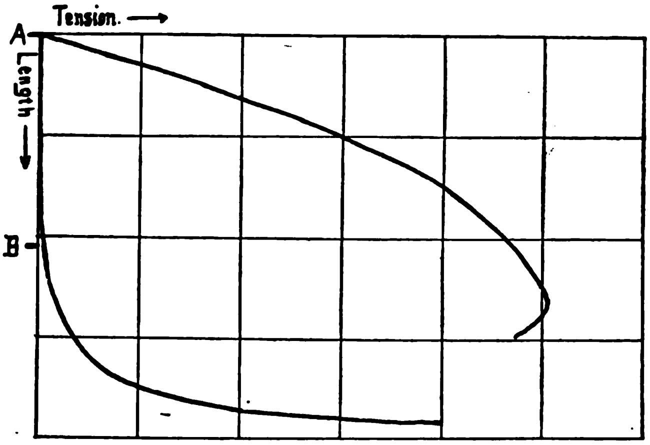


Fig. 1.—Curve Showing the Relation of the Initial Length to the Tension and Energy Set Free during an Isometric Twitch of a Voluntary Muscle. (A) Represents the Maximum Shortening of the Muscle and (B) Its Maximum Length in the Body. The Curve on the Left Represents the Relation between the Length and the Tension when the Muscle Is Relaxed. The Curve on the Right Represents This Relation when the Muscle Is Contracted. The Changes in Tension during an Isometric Contraction Are Represented by Horizontal Lines Drawn between the Two Curves at any Initial Length. The Changes in Length during an Isotonic Contraction Are Approximately Proportional to the Vertical Distance between the Two Curves. Note that Within Physiological Limits the Contractions of the Muscle Increase with its Initial Length. (Redrawn from a Figure of Patterson, Piper and Starling, Based on the Results of an Experiment of Blix, Jour. Physiol.)

beyond the normal physiological length of the muscle. The energy evolved during a contraction also becomes greater when the initial length of the muscle is increased.

Isotonic Excursion.—The height of isotonic contractions of the muscle at different initial lengths is also roughly represented on this diagram, for the height of a single twitch contraction is somewhat less than the vertical distance between the two curves. Within limits an increase in the initial length of the muscle will, therefore, cause a greater excursion of the ensuing contraction.

Combined Contraction.—The contraction of the cardiac muscle is neither a pure isometric contraction nor a pure isotonic contraction, but is a combination of the two. At the onset of ventricular systole the valves leading into the auricles close, and the first portion of the contraction takes place with a rise of intraventricular pressure, but with no expulsion of blood. It is an isometric contraction. When the intraventricular pressure rises sufficiently to open the semilunar valves, the left ventricle empties its contents more or less completely into the aorta, and at a pressure that corresponds approximately to the arterial blood pressure. The ventricular contraction at this time is predominantly an isotonic contraction.

The ventricular systole may be compared with the contraction of an "after-loaded" voluntary muscle, where the main weight is artificially supported during the muscular relaxation, but is lifted during its contraction. During relaxation the tension of the muscle is determined solely by its length. When it contracts the muscular tension rises, but at first there is no shortening of the muscle (isometric period). After the tension has increased sufficiently to raise the weight, the muscle begins to shorten and the remainder of the contraction is approximately isotonic. As Henderson has pointed out, the conditions under which the heart

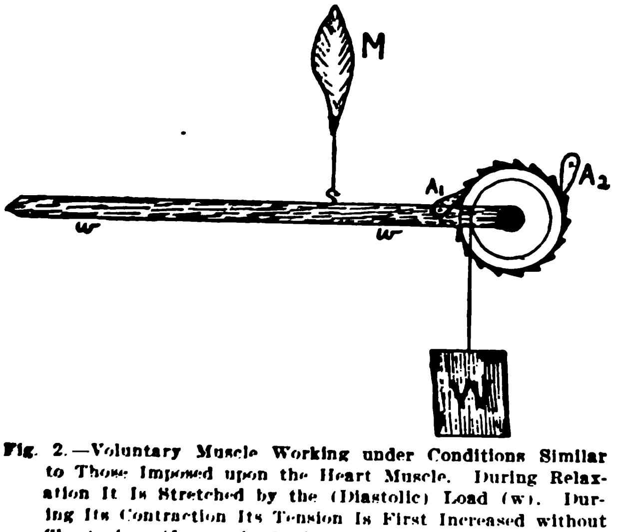


Fig. 2.—Voluntary Muscle Working under Conditions Similar to Those Imposed upon the Heart Muscle. During Relaxation It Is Stretched by the (Diastolic) Load (w). During Its Contraction Its Tension Is First Increased without Shortening (Isometric Period). When the Tension Has Increased Sufficiently It Lifts the Heavy Load (W) Expulsion of Blood Against the High Arterial Pressure. (From Patterson, Piper and Starling. Jour. Physiol.)

works may be duplicated for the voluntary muscle by having it raise a weight that is supported during relaxation by a ratchet (Fig. 2).

Fiber Length and Linear Tension.—In the heart there is no direct method for measuring either the length of the muscle fibers or the linear tension to which they are subjected. Since, however, the size of the ventricular cavity determines the length of the muscle fibers, and the intraventricular pressure determines the linear tension, the relation between ventricular volume and intraventricular pressure corresponds to the relation between the length and tension of a voluntary muscle. The relation

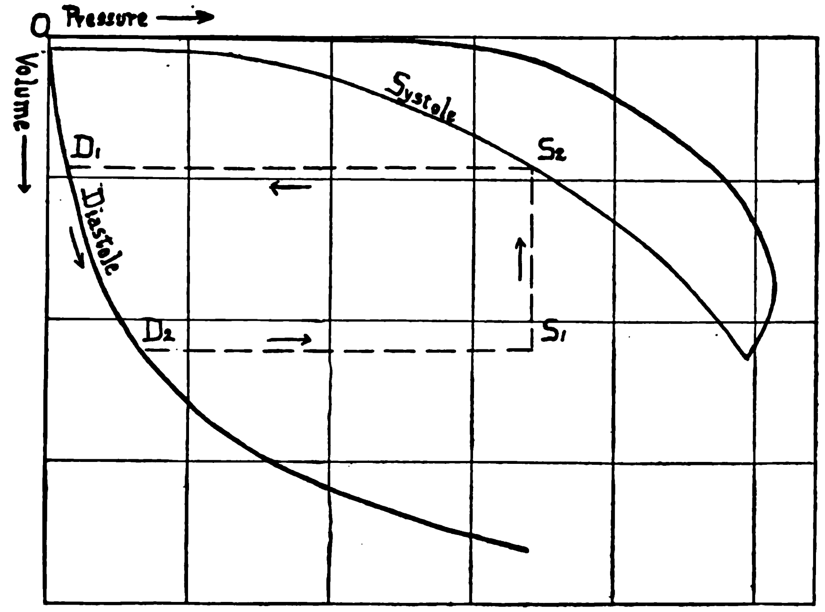


Fig. 3.—Schematic Relation between the Volume and the Intraventricular Pressure during Diastole (Curve to Left) and during Systole (Curves to Right), Based on Frank's Diagram. At the Onset of Diastole the Ventricle Relaxes and Assumes the D_1 Position. As the Blood Enters, the Volume Increases with a Relatively Small Rise of Pressure to D_2. The Onset of Systole Alters the Properties of the Heart Muscle So That They Correspond to the Systolic Curve. The Heart Muscle Therefore Contracts, First Isometrically (D_2 to S_1) and Then Isotonically (S_1 to S_2). This Contraction Is Short of That Theoretically Possible, the Latter Being Indicated by the Upper of the Two Upper Curves.

between these two variables, as determined by Frank for the frog's heart, is shown in Figure 3.

Diastolic and Systolic Volume.—During diastole the size of the ventricular cavity is determined by the tone of the relaxed muscle and the pressure of the entering blood stream. An increase in diastolic volume may be due either to a loss of diastolic tone or to an increase in the filling pressure. The latter, according to Wiggers, varies from 2 to 6 mm. of mercury in the right ventricle of the mammalian heart. Dur-

ing systole, on the other hand, the size of the ventricular cavity is governed by the systolic tone of its muscle, and by the pressure against which its contents are expelled. An increase in the systolic volume may be due either to a loss of systolic tone or to an increase in arterial pressure.

Reaction to Varying Arterial Resistance

In order to study the reaction of the heart muscle during variations in filling and in arterial resistance it is necessary to control: (1) the rate of the heart beat: (2) the blood supply to the heart: and (3) the arterial tension. The dynamics of the mammalian heart have been studied by

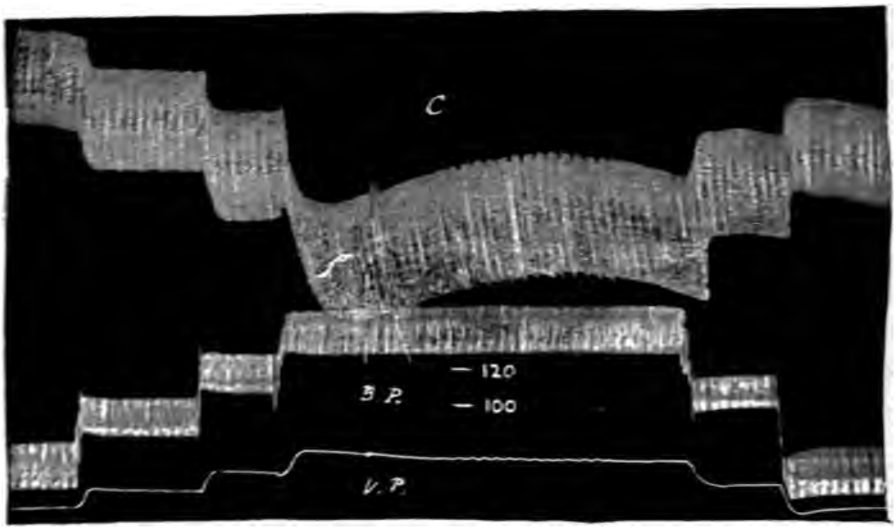


Fig. 4.—Effect of Raising and Lowering the Arterial Resistance upon the Volume and Output of the Ventricles in the Heart-lung Preparation. C Is the Cardiac Volume, the Downstrokes Representing Increases of Volume. B. P. Is the Blood Pressure. V. P. Is the Venous Pressure. Note That a Rise of Arterial Resistance Causes an Increase in the Volume of the Ventricle and a Rise of Venous Pressure But That the Cardiac Output (Excursion of C) Remains Constant at Different Levels of Arterial Pressure. (From Patterson, Piper and Starling, Jour. Physiol.)

Straub, Starling, and others by means of the "heart-lung" preparation. In such a preparation the perfused fluid flows through an unaltered pulmonic circuit. The arterial resistance as well as the inflow to the right auricle is controlled mechanically. The heart rate is governed partly by the temperature of the perfusion fluid, and partly by stimulation of the extrinsic cardiac nerves.

Using such a preparation Starling and his associates found, that with a constant heart rate the ventricular volume increases with each rise of the arterial pressure and diminishes with each fall, even though the output remains practically constant after the new conditions have become

established (Fig. 4). The primary ventricular dilatation after an arterial increase in pressure may be followed by some recovery, but the volume always remains greater at high than low pressure.

The immediate result of a rise in arterial pressure is a transient diminution in the systolic output, so that the ventricle fails to put out all of the blood coming to it. The volume of the ventricle, therefore, increases and the venous pressure becomes greater. But this enlargement of the ventricle during diastole lengthens the muscle fibers and increases their tension, and these changes, as we have seen, tend to cause a more powerful systole. After a few beats, therefore, the ventricle puts out the usual amount of blood against the increased arterial resistance. The physiological dilatation of the ventricle enables the muscle to develop greater energy, and the inflowing blood is expelled even though the blood pressure is raised. The physiological dilatation of the ventricle has acted as a compensatory process, which enables the heart to accomplish the extra work demanded of it.

Reaction to Varying Inflows

In other experiments Starling and his associates maintained the arterial pressure at a constant level, but varied the rate at which the blood entered the auricles. It was found that, under these conditions, the heart is capable of putting out widely varying amounts of blood. If the venous inflow be increased the ventricles are better filled during diastole. At this time the tension of the muscle is slight, and the ventricle takes up the extra blood coming to it with but a small increase in tension. The muscle fibers, being lengthened and more tense, show a larger excursion during their subsequent contraction, just as happens when the voluntary muscle is moderately extended during its period of relaxation. The output from the heart is, therefore, increased and it soon becomes equal to the inflow. The effect of varying the inflow upon the size and output of the ventricles is shown in Figure 5. It will be noted that the systolic as well as the diastolic volume of the ventricle increases when larger amounts of blood are being pumped. Apparently the ventricles not only dilate during diastole in order to take up the extra blood coming to them, but they do not contract so perfectly when the cavities contain large amounts of blood. The output, however, is increased.

Control of Heart Output.—From what has just been said, it is obvious that the output from the heart is governed not so much by the arterial resistance to be overcome as by the amount of blood that enters from the veins. When the venous pressure is increased, more blood enters the heart during diastole, and the increased length and tension of the muscle fibers cause them to contract with greater energy. This may serve to maintain the usual output against a heightened arterial pressure, or it

may serve to expel an increased amount of blood against the normal arterial resistance. In either case, the systolic as well as the diastolic volume of the ventricle tends to increase.

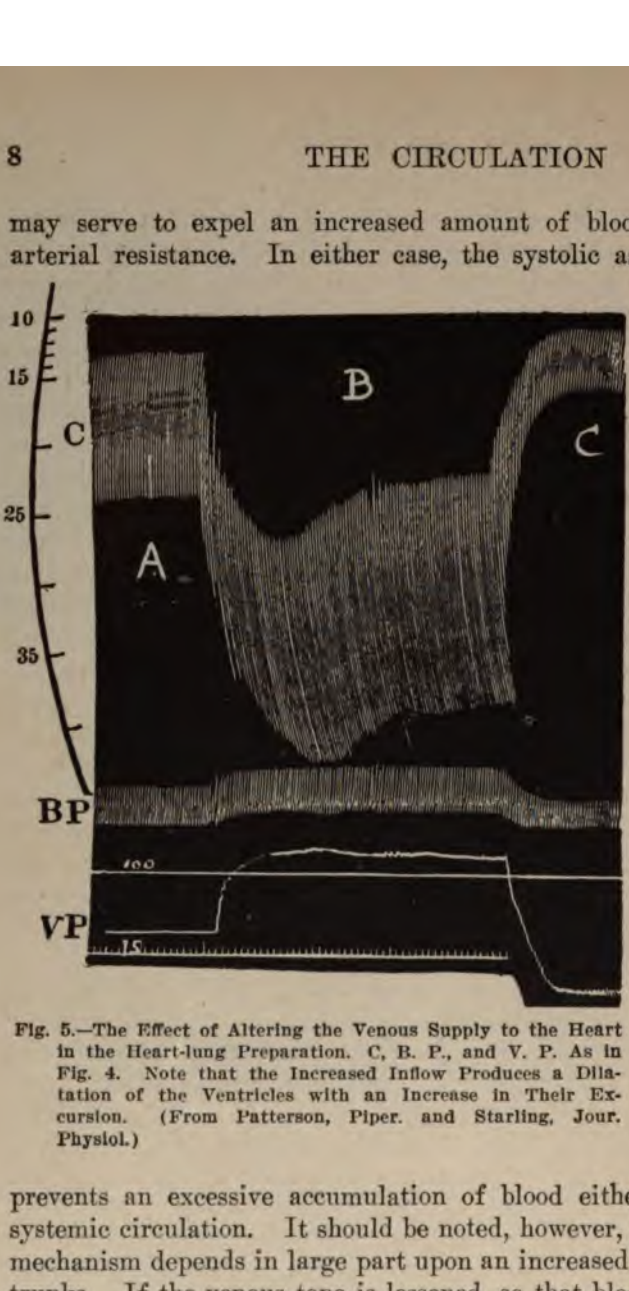


Fig. 5.—The Effect of Altering the Venous Supply to the Heart in the Heart-lung Preparation. C, B. P., and V. P. As in Fig. 4. Note that the Increased Inflow Produces a Dilatation of the Ventricles with an Increase in Their Excursion. (From Patterson, Piper, and Starling, Jour. Physiol.)

Equalizing Mechanism. — The mechanism which equalizes the output from two sides of the heart under the conditions of Starling's experiment is now clear. If, for any reason, one side is given an increased amount of work to do, either by reason of an increased arterial pressure or by reason of an increased inflow of blood, it responds by a physiological dilatation of its cavity with increase in the diastolic length and tension of the muscle. This physiological dilatation enables it to meet the new requirements, and prevents an excessive accumulation of blood either in the pulmonic or systemic circulation. It should be noted, however, that this compensatory mechanism depends in large part upon an increased pressure in the venous trunks. If the venous tone is lessened, so that blood collects in the veins without an increase in venous pressure, the output from the corresponding ventricle may not be increased.

Influence of the Heart Rate

In the heart-lung preparation, the heart rate may be slowed either by cooling the perfusion fluid or by stimulating the vagus nerve. When the heart is cooled, the longer diastole allows a more complete filling of the ventricle during its relaxation. The diastolic volume of the ventricle is increased and the output at each beat is also augmented. This may

neutralize the effect of the slow heart rate so that the output per minute varies but little from that present when the heart is beating rapidly. Within limits, therefore, the output in a given time is not necessarily changed by variations in the heart rate, for the heart continues to expel the blood that comes to it, and the changes in rate may be compensated for by changes in the output at each beat.

Vagus Influence.—When the heart is slowed by vagus stimulation the same conditions prevail, except that the ventricles are markedly distended in both systole and diastole, probably because the vagus nerve influences the tone of the heart muscle. This change in volume is of more than passing interest, because variations in the heart rate of man are commonly caused by variations in vagus activity. With vagus slowing of the rate, therefore, one would expect an increase in both the systolic and diastolic heart volumes, and with an acceleration of the rate from vagus inhibition a lessened size of the heart in both positions.

Effect of Diastolic Tone.—By the diastolic tone of the heart muscle we mean the amount to which the muscle fibers are lengthened by a given intraventricular pressure during diastole. Changes in tone are undoubtedly produced by vagus and other influences. When the tone is diminished the diastolic relaxation of the heart will be increased and the dilatation thus produced will differ from that caused by an increased flow of blood in that the cardiac output is not necessarily increased. These two factors, cardiac tone and venous inflow, together determine the size of the cardiac cavities during diastole.

Diastolic Relaxation.—According to Henderson, the output from the ventricles under normal conditions depends not so much upon the supply

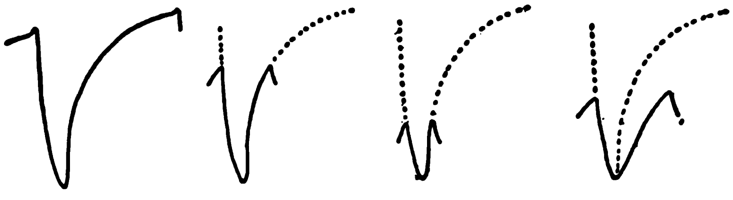


Fig. 6.—Schematic Representations of Henderson's Conception of Diastolic Filling of the Ventricles. Downstrokes Represent Systole, Upstrokes Diastole. In (A) the Heart Action is Slow and Diastolic Filling Is More Complete Than during Rapid Heart Action, (B) and (C). The Latter Follow only a Part of the Complete Curve. In (D) the Diastolic Filling Is Abnormally Slow and the Systolic Discharge for this Heart Rate Is Thereby Lessened. (From Henderson, Am. Jour. Physiol.)

of blood to the heart as upon the form and duraton of the diastolic relaxation. Henderson believes that ventricular diastole in a given heart always follows a uniform curve. At first it is rapid and then gradually, or rather suddenly, becomes much slower (Fig. 6). He believes, furthermore, that the pressure in the systemic veins usually suffices to fill the

right ventricle as rapidly as the latter relaxes, and that any increase of venous pressure above this "critical" limit does not influence ventricular filling. Only when the venous pressure is pathologically lowered, as in shock, does it diminish the output from the ventricle. A logical consequence of Henderson's hypothesis, that the diastolic relaxation of a given heart always follows a uniform curve, is that the volume output during systole is determined by the form of the relaxation curve and the duration of diastole. Whenever diastole is shortened less blood is put out in the succeeding systole. Since, however, relaxation is more rapid in early diastole, an increase in heart rate will, within limits, cause an increase in the output per minute. Conversely, slowing of the heart rate increases the output at a single beat but diminishes the output per minute. Henderson's views are opposed by those who have studied the dynamics of the heart in the heart-lung preparation. They also do not accord with the view that during exercise the outpptt at each ventricular systole may be increased even though the heart rate is accelerated. (See Effect of Exercise.)

The Normal Heart Shadow in Man

The volume of the heart is determined in part by the thickness of its walls and in part by the size of its cavities. No direct measurements of these separate factors are possible in the living subject. The most accurate data with regard to the size of the heart in the living human subject are derived from x-ray studies. By this means the area of the heart shadow may be accurately determined. The effects of divergence in the rays are eliminated either by using the orthodiagraph or by placing the Röntgen tube at a considerable distance from the body. The records thus obtained do not permit an estimate either of the thickness of the muscle walls, or of the size of the individual cardiac chambers.

Individual Variations.—Orthodiagraphic studies have shown that, in a general way, the size of the heart shadow in different normal individuals increases with the height and the weight of the individual observed.

Diminution.—In a given man the size of the heart shadow may vary considerably under physiological conditions. The shadow outlines are determined mainly by the diastolic volume of the heart. When the heart is beating more rapidly and the diastolic filling is shortened, the cardiac shadow will therefore tend to be smaller. As a matter of fact, the rapid heart rate produced by the administration of *atropin* is usually associated with a diminution in the area of the heart shadow. This is caused not alone by the rapid heart action, but is due in part to the increased tone of the heart muscle during vagus paralysis. During marked pathological increases in the heart rate, such as occur in *paroxysmal tachycardia* (q. v.), the heart shadow, according to Dietlen, also becomes smaller.

From Changed Position.—The heart shadow becomes distinctly

smaller when an individual passes from the recumbent to the upright position. This change is due in part to the increased heart rate. In part it is probably due to a lessened blood flow to the right auricle, owing to a greater collection of blood in the splanchnic vessels.

After Exercise.—After exercise the silhouette of the human heart is usually smaller than before, a fact that has now been established by numerous x-ray observations. This diminution in size is due in part at least to the more rapid heart rate, which, as we have seen, always tends to cause a considerable diminution in the diastolic volume of the heart. Only in patients with cardiac disease is there at times a definite increase in the heart shadow after exercise. The effect of exercise upon the circulation will be discussed more fully in succeeding paragraphs; but it may be pointed out here that most of the observations dealing with the effect of exercise upon the size of the heart shadow have been made, not during, but shortly after the exertion. It is by no means improbable that the cardiac volume changes rapidly when the exertion is over, and that during the exertion itself the diastolic volume may be normal or slightly increased.

Incompleteness of Ventricular Systole

In *physiological experiments* it is not uncommon to find that considerable residues of blood have been left in the ventricles at the end of systole. In Figures 4 and 5, for example, it will be seen that when the blood pressure or the cardiac output has been increased, the systolic volume of the ventricles may exceed the diastolic volume in other parts of the tracing. It is obvious that, under such experimental conditions at least, the ventricles may contain very considerable quantities of blood, even at the end of systole.

So far as *man* is concerned, we have no direct evidence that the ventricles ordinarily contain any considerable residue of blood at the end of systole; yet various observations with the x-ray indicate that such is, in all likelihood, the case. When the thorax is examined by means of a fluoroscopic screen, the ventricular movements during systole appear so slight, that it hardly seems possible that the ventricular cavities are emptied at each stroke. Furthermore, Moritz has observed that when a young and slender individual passes from the recumbent to the upright posture, the decrease in the size of the heart shadow may be so marked, that the systolic outline when recumbent is greater than the diastolic outline when upright. Considerable variations in the size of the heart shadow may also be produced by a Valsalva experiment, or by hot or cold baths. The interpretation of such changes is rendered uncertain, because the area of the heart shadow is determined not by the volume of the ventricles alone, but by the position of the heart and by the

size of the right auricle. Even though one admit this possible error, nevertheless it seems probable that in the normal man, as in animal experiments, there is often an appreciable, or even a very considerable residue of blood left in the ventricular cavities at the end of systole, and that this residue is liable to considerable fluctuations under normal as well as under pathological conditions.

Dynamics of the Weakened Heart

When a voluntary muscle that is executing isometric contractions begins to tire, the fatigue becomes evident by the fact that the muscle no longer develops the same tension for a given initial length. If, however, the initial length be somewhat increased, the fatigued, like the normal, muscle develops a greater energy of contraction. Let us assume, for example, that a normal muscle with an initial length of 2 cms. develops a tension of 50 grams when contracted, and that the same muscle, at the same initial length, develops a tension of 30 grams when fatigued. If the fatigued muscle be now stretched to a length of 3 cm. it may develop a tension of 50 grams during contraction. The stretching has enabled it to develop a tension equal to that previously developed by the normal muscle. It is obvious, however, that when the initial lengths are the same the fatigued muscle develops less energy than the normal muscle, and that, furthermore, there is always a limit beyond which stretching of the muscle will not increase its energy. If this limit be approached, the maximum tension possible will be found to be greater for the normal than for the fatigued muscle. In other words, the potential capabilities of the normal muscle are greater than that of the fatigued muscle, even though they may both be doing the same work under the conditions of such an experiment.

Weakened Ventricular Muscle.—The properties of the fatigued voluntary muscle with its lessened capabilities under given conditions are probably not unlike the properties of a weakened heart muscle. When the ventricular muscle is weak the ventricles expel their contents less perfectly against a given arterial pressure and, consequently, the systolic volume of the heart is greater than normal. To this increased systolic residue there is added the blood which enters from the veins during diastole, and it is obvious that the diastolic volume of the ventricle will also tend to be increased. Within limits, however, this increase in the ventricular volume during diastole is advantageous, for a lengthening of the muscle fibers enables the weakened heart muscle to develop greater energy, just as the fatigued voluntary muscle develops greater energy when it is further extended. In consequence of this greater energy the weakened heart may, within limits, maintain a normal circulation. It pumps the usual amount of blood and maintains the usual arterial blood pressure. The only objective evidences of weakness may be a moderate dilatation

of the ventricular cavities and possibly also a slight rise of venous pressure. Such a dilatation, though evidence of weakness, is in itself a favorable and compensatory reaction, for it enables the weakened muscle to carry on the circulation. We have said that, within limits, the weakened heart muscle may carry on a normal circulation, both as regards the arterial pressure maintained and the amount of blood pumped. The limits of capability are, however, always less than the normal. When, as in muscular exercise, the arterial pressure is raised and unusual quantities of blood must be pumped, the weakened muscle is unable to do the work required of it, and the weaker the muscle the narrower will be its range of capabilities.

Pressure and Distensibility.—The relationship between the normal and the weakened muscle is represented schematically in Figure 7.

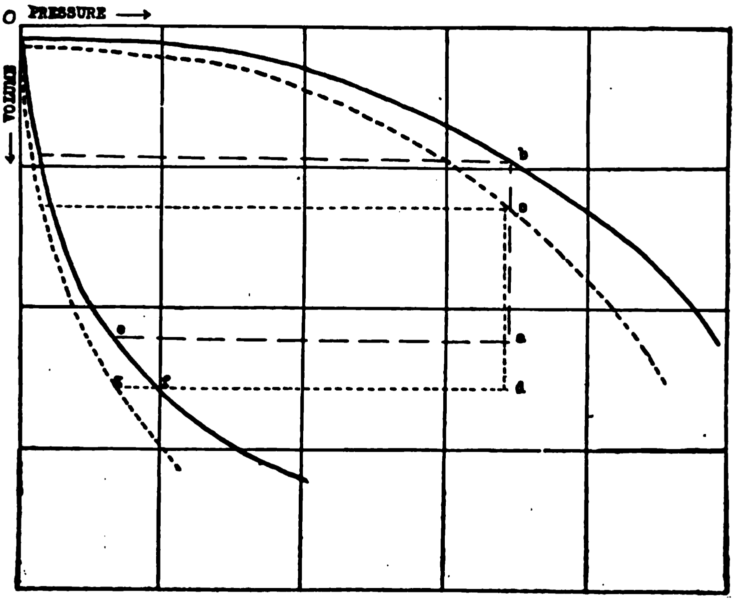


Fig. 7.—Schematic Representation of the Relation between the Normal and Weakened (Atonic) Heart Muscle. The Heavy Solid Lines Represent the Normal Muscle and the Course of Contraction Is Represented by e, a, b, Just As in Fig. 3. The Broken Lines Represent the Weakened Heart Muscle. It will Be Seen that by Dilating, this Muscle Is Able to Put Out the Same Amount of Blood against the Same Arterial Pressure as the Normal Heart. Furthermore, If the Curve of Diastolic Tone Follows the Dotted Line, There Is No Rise of Diastolic or of Venous Pressure.

The upper of the continuous lines, taken from Frank's curve for the frog's ventricle, represents the relation between the volume of a normal ventricle and the pressure developed during its contraction. The broken curve just below is drawn to represent this relation for the weakened ventricle. If the output during ordinary conditions of life be represented by the line *a b*, then it will be seen that the same volume, *c d*, may be put

out by the weakened heart at the same arterial pressure. In the latter case, however, the size of the heart is increased in both systole and diastole. The pressure during diastole and with this the venous pressure depend largely upon the distensibility of the ventricular muscle during diastole. This is represented by the lower curves. If this diastolic distensibility remains unaltered in cardiac weakness, then the diastolic and venous pressures are raised as a result of weakness of the heart muscle (tension at *f* is greater than tension at *e*). Such an increase is not necessary, however, for it is possible that the increased distensibility during systole which characterizes the weakened heart muscle is associated with an increased distensibility during diastole. If this be the case, then the venous pressure may not be increased, so long as the weakened heart is competent to do the work required of it (tension at *g* equals the tension at *e*). The diagram also shows that the range of accommodation of the

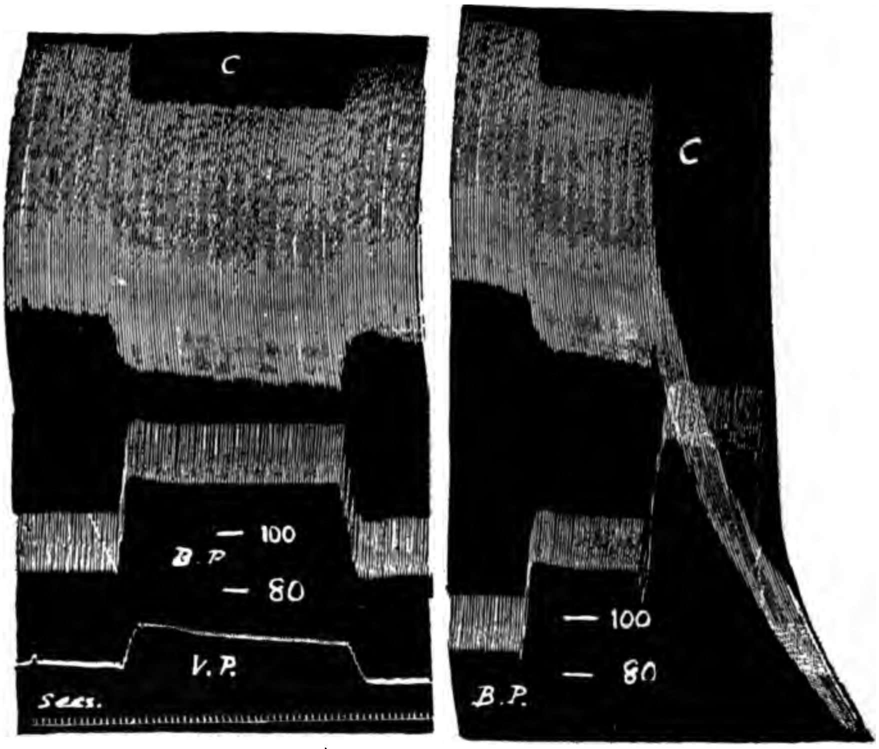


Fig. 8.—Compensatory and Excessive Dilatation from Raising the Blood Pressure in a Heart-lung Preparation. In the Figure on the Left the Rise of Pressure (B. P.) Causes a Dilatation of the Ventricles (Downward Movement of C), But They Then Continue to Pump Out the Blood Coming to Them. In the Figure on the Right the Further Rise of Arterial Pressure Causes a Further Ventricular Dilatation Which Rapidly Increases Because the Ventricles Can No Longer Pump Out the Blood Coming to Them Only Prompt Measures Could Check This Acute Dilatation. (Reproduced from Patterson, Piper and Starling, Jour. Physiol.)

weakened muscle is less than that of the normal muscle. The maximum pressure that may be overcome is less, and the maximum output that may be attained against lower pressures is also probably less.

We have spoken thus far of the favorable effects of a moderate "compensatory" dilatation upon the dynamics of the heart. There is obviously a limit to the favorable effect of dilatation, however, and it is common knowledge that cardiac failure is usually associated with a marked dilatation of the heart. If the arterial pressure be gradually and continuously increased, a time will come when the ventricle is no longer capable of putting out all of the blood coming to it. There will then result a gradually increasing dilatation, owing to the continued and growing discrepancy between the ventricular output and the venous inflow (Fig. 8). Such a dilatation is, of course, incompatible with life, and the ventricle can recover only if the arterial pressure be lowered or the venous inflow be reduced.

Causes of Cardiac Weakness

(a) Fatigue

When a voluntary muscle is made to execute a rapid series of contractions it does not have time to recuperate during the pauses, and fatigue with gradual loss of power sets in. Fatigue is more readily produced when there is an imperfect removal of waste products, or an insufficient supply of oxygen and nutrient material, all of which accompany deficient circulation through the muscle. Fatigue passes off if the muscle be allowed to rest, and it passes off more promptly if at the same time a good circulation be maintained.

Normal Heart Muscle.—The conditions in the heart muscle are obviously different from those in a voluntary muscle. Ordinarily the heart recuperates completely during the diastolic pause that succeeds each contraction. The work of the heart is increased very markedly during violent muscular exercise, for increased amounts of blood are pumped against a heightened blood pressure (page 25). Yet there is, as a rule, no evidence of cardiac fatigue, for very shortly after the most strenuous exertion the shadow of the normal heart is usually diminished rather than increased, and insufficiency rarely occurs. With a normal heart muscle, therefore, it would seem that the general fatigue which follows violent exercise is due, not to fatigue of the heart, but to fatigue of the voluntary muscles used during the exercise.

Weakened Heart Muscle.—We have seen, however, that if a voluntary muscle is insufficiently supplied with blood, it is fatigued by amounts of work that could ordinarily be performed without tiring. Similarly, when the heart muscle receives a poor blood supply, or when for some other reason it is already weakened, prolonged exercise may be followed by cardiac dilatation, and by a lessened working capacity that may persist

for a longer or shorter interval. Such dilatation and weakness as a result of prolonged work evidently have much in common with the fatigue of a voluntary muscle. Until more is known of the chemical and physiological changes during fatigue, however, the exact relation cannot be more definitely stated.

(b) Functional Insufficiency

The weakness that develops when certain hearts are called upon to meet the demands of prolonged muscular exercise, shades imperceptibly into the weakness that is present constantly, even when no special demands are made upon the heart. Such weakness may, or may not, be associated with demonstrable anatomical changes in the muscle. Thus a sudden diminution in the blood supply to the myocardium may cause an acute cardiac insufficiency before anatomical changes in the muscle have had time to develop. A less marked but more prolonged interference with the coronary circulation may, in all probability, cause muscular weakness with little if any anatomical change. In severe anemias (Moritz), and during acute infections (Dietlen), there may be a transient enlargement of the heart shadow, for the reason that lack of oxygen or the presence of toxic substances has weakened the myocardium.

In such cases as well as in cachexias, inanition, etc., the anatomical changes in the muscle often seem insufficient to account for the weakness or dilatation observed clinically.

(c) Anatomical Changes in the Myocardium

The relation between cardiac weakness and anatomical changes in the heart muscle is, in certain instances, an obvious one. A disappearance of muscle fibers with an increase in connective tissue can only lead to impaired function. Loss of muscle striations and imperfect staining of the muscle nuclei also indicate an impairment of muscular efficiency. In certain infectious diseases and particularly in acute rheumatic fever, definite changes have been found in the muscle fibers or interstitial tissue which suffice to explain the functional changes observed clinically.

Fatty Changes.—On the other hand, anatomical alterations may be present in the heart muscle when there is little if any evidence of functional impairment. Thus, cloudy swelling is not infrequently found in hearts that have shown no clinical evidence of insufficiency. The significance of "fatty degeneration" of the muscle fibers has been much discussed. Virchow's hypothesis, that the fat visible in such fibers was derived from a breaking down of muscle proteins, necessarily led to the assumption that fatty degeneration caused muscular weakness. It now seems certain, however, that this fat is derived either from fatty deposits elsewhere in the body, or from fatty substances previously present in the heart muscle but not demonstrable by microscopic methods. There is, therefore, no

longer a logical necessity for believing that fatty degeneration is a sign of serious muscular weakness. At the same time, the two may well go together. When marked fatty degeneration has been produced in animals by experimental phosphorus poisoning, the strength of the heart muscle (in the frog) is diminished and the hearts of dogs show an unusual tendency to cardiac dilatation as a result of exercise (de la Camp). Such marked fatty changes are, however, uncommon in patients dying of cardiac insufficiency, and it is by no means certain that the lesser grades of fatty degeneration seen at autopsy cause a serious myocardial weakness.

Circulatory Changes.—The heart muscle is very sensitive to changes in its blood supply. This has been abundantly proven by experimental investigations, and it is well known that disease of the coronary arteries is one of the most important causes of myocardial weakness in man, and particularly in the later decades of life. A lessened blood supply diminishes the working capacity of the muscle even though no anatomical changes are present. But changes in the structure of the heart muscle frequently accompany coronary sclerosis. When the blood supply is poor the muscle fibers may show nutritional changes, and an increased growth of connective tissue may take place. When the blood is entirely shut off from small areas of the myocardium there result local necroses with secondary scar formation. When the circulation is shut off from an extensive area the subsequent necrosis may lead to an aneurism or rupture of the heart wall. It is evident, therefore, that changes in the coronary circulation may produce insufficiency, both through readily demonstrable anatomical alterations, and through less evident nutritional disturbances of the heart muscle.

Cardiac Dilatation

In the heart-lung preparation, as we have seen (page 6), a dilatation of the ventricles may be caused either by a weakening of the muscle with lessening of the ventricular tone, or by an increase in the demands upon the heart. The physiological dilatation that accompanies a rise of arterial pressure or a rapid inflow of venous blood is of a compensatory character, for it enables the ventricle to do the extra work demanded of it. In man also transient changes in the size of the heart may result from transient muscular weakness, or from transient increases in work. Under pathological conditions, the muscular weakness or the increase in work may be continuous rather than transient, and one would, therefore, expect that a continuous dilatation of the ventricles would result.

Increased Work.—Of pathological conditions in which the left ventricle is called upon to do an increased amount of work over long periods of time, the most important are continued arterial hypertension, aortic lesions, and mitral insufficiency. The effect of these conditions upon the left ventricle will be discussed more fully under the appropriate headings,

but it may be pointed out here that, in aortic as in mitral insufficiency, the left ventricle is required to pump unusual quantities of blood at each stroke. These valvular lesions are almost invariably accompanied by a dilatation of this chamber, and this dilatation plays an important part in the maintenance of the circulation. It is, therefore, the type of a favorable or compensatory dilatation.

In aortic stenosis and in chronic arterial hypertension, on the other hand, the quantity of blood pumped is not increased but the resistance opposed to the emptying of the left ventricle is greater than normal. In the heart-lung preparation such an increase in resistance also causes a compensatory dilatation of the ventricle. Possibly, however, such a dilatation does not occur in the intact animal, for Hirschfelder found that the ventricle of a dog's heart may overcome a heightened blood pressure with no increase in its size. It is probable that in man also the left ventricle may under unusually favorable circumstances overcome a high resistance without dilatation. In the earlier stages of aortic stenosis and chronic hypertension no dilatation of the left ventricle may be present. Under less perfect conditions, however, the left ventricle probably dilates somewhat, just as it does in the heart-lung preparation. The dilatation of the left ventricle that is not uncommonly observed in patients suffering from chronic hypertension may be in part similar to that which occurs in the heart-lung preparation. It enables the ventricular muscle to put forth greater effort and is, therefore, in a certain sense compensatory in character.

Loss of Tone.—Cardiac dilatation may also result from loss of muscular tone. The dynamics of the weakened heart muscle have already been discussed and need only be referred to in this place. It will be recalled that a weakening of the heart muscle leads to a dilatation of the ventricular cavity, but that in consequence of this dilatation the muscle may be able to expel the usual amount of blood against the usual blood pressure. Only when unusual demands are made upon such a heart do its limitations as compared with the normal become apparent.

Physical and Structural Changes in Heart Muscle.—Finally, cardiac dilatation is favored by physical or structural changes in the heart muscle. For example, a long-continued strain or a long-continued weakness causes a prolonged dilatation. As a result the muscle may become fixed in the new position, so that even though the strain be relieved or the muscular weakness disappear the ventricle remains permanently larger than before. Dietlen has observed, for example, that the dilatation of the heart during acute infectious diseases usually undergoes only a partial retrogression after recovery, the heart shadow being left permanently larger than before. Dilatation of a ventricular cavity ordinarily accompanies an hypertrophy of its walls. In many cases increased work is the common cause of both, or, again, the dilatation is due to a

weakness of the hypertrophied muscle. It seems not improbable, however, that the mass thickening of the muscle wall may in itself lead to an enlargement of the enclosed cavity.

Excessive Dilatation.—The types of dilatation discussed thus far are associated with a more or less perfect maintenance of the circulation. The heart pumps on the blood that comes to it and there is no necessary alteration in either the venous or arterial pressures. A temporary increase of work leads to a further but temporary increase in the size of the heart, which within limits aids the cardiac contractions. If, however, the acute dilatation exceed a certain limit it may exert a very unfavorable effect upon the cardiac function. Excessive dilatation lessens the contractile force of the muscle and the changes that characterize acute cardiac failure then supervene. The dilated ventricle fails to expel the blood coming to it, the venous pressure rises, and this in turn tends to distend the ventricular cavity still further during diastole. If the acute dilatation has been induced by sudden exertion or by a sudden increase in the arterial blood pressure, perfect rest or a reduction of the arterial pressure may allow the burdened ventricle to pump out the accumulated blood and to recover its previous size. If, however, the demands are not reduced below the functional capacity of the weakened muscle, the continued collection of blood in the dilated ventricle leads to a cardiac death.

Hypertrophy of the Heart

It is common knowledge that when a voluntary muscle is exercised it grows larger. This hypertrophy is due mainly to an increase in the size of the individual muscle fibers. At the same time the strength of the muscle increases. Heavier loads than before can be lifted and more work can be done without fatigue.

The heart muscle also hypertrophies as a result of increased work, the hypertrophy again being due mainly to an increase in the size of the individual muscle fibers. The hypertrophied heart also possesses a greater working capacity than the normal. The maximum pressure attainable on clamping the aorta is increased, and, at a given arterial pressure, more blood can be pumped without developing insufficiency. Not only may hypertrophy involve the heart as a whole, but it may involve the musculature of individual cardiac chambers. When additional work is done by only one chamber, the muscle surrounding this hypertrophies, while the remainder of the heart is affected to a lesser extent if at all.

The Weight of the Heart

When the heart is markedly hypertrophied, the change is obvious on inspection. Minor changes, however, are less easily determined, for the

amount of heart muscle varies considerably in different normal individuals. An approximate standard is furnished by comparing the size of the heart with the size of the subject's right fist. Any accurate estimate of the amount of heart muscle, however, can be obtained only by weighing, the most exact method being that used by W. Müller. According to this method, the heart muscle is first freed from the non-muscular tissues and is then divided into pieces, so that the weight of the different cardiac chambers can be calculated. Each piece is then weighed and the results are added. Such a method determines not only the total weight of the heart muscle, but also the absolute and relative weights of its constituent portions.

Heart-Body Ratio.—Müller found that the weight of the entire heart increased with the weight of the body, but that the proportion between the two tended to diminish as the body weight increased.

Müller's Table (from Grober)

Body Weight in Kilograms	Absolute Weight of Heart in Grams	Ratio to Body Weight Milligrams per Gram
1–10	28.9	5.87
10–20	78.0	5.20
20–30	133.5	5.49
30–40	193.3	5.47
40–50	230.2	5.10
50–60	264.3	4.81
60–70	297.2	4.45
70–80	322.3	4.37
80–90	359.0	4.28
90–100	376.3	4.01
100–110	358.5	3.46

The above table may be used as a standard for determining whether a given heart is larger or smaller than the average. It should be remembered, however, that there are considerable individual variations from these average figures. In particular, it seems certain that of two individuals weighing the same, the one who is accustomed to do heavy work will have the larger heart; or again that the one who is tall and slender will have a larger heart than the one who is short and fat. Undoubtedly, therefore, it would be more exact to compare the weight of the heart, not with the weight of the body as a whole, but with the weight of its active tissues after eliminating the weight of the fat, the bones, etc., as well as that due to edemas or exudates. Such accurate measurements are, however, hardly possible at autopsies, so that our most accurate standard is the ratio between the heart weight and the body weight after

making some allowance for the amount of inactive tissue in the body. If this ratio between the heart and the body weights be excessive the heart is said to be hypertrophied.

Strength of the Hypertrophied Heart Muscle

We have expressed the view that, when the heart muscle hypertrophies as a result of increased work, its strength is greater than before, and that it can now accomplish a given amount of work with greater ease, or can, when necessary, overcome a greater resistance than it could previously. This view is based, in part, upon the analogous increase in the working capacity of the hypertrophied voluntary muscle. In part, it is based on the fact that the heart of the trained athlete meets the demands made upon it with relative ease, and that the hypertrophied heart in valvular disease may under favorable conditions perform the extra work resulting from the valvular defect with no apparent difficulty. Finally, Hasenfeld and Romberg have studied the reserve force of the left ventricle in experimental aortic insufficiency, and have concluded from their experiments that, when the ventricle has been given time to hypertrophy, it can carry on the circulation and meet unusual demands better than the normal ventricle can immediately after the lesion has been produced.

Weight and Strength.—It must be admitted, however, that, even under favorable conditions, the strength of the hypertrophied heart muscle does not necessarily increase in proportion to the increase in its weight. It is obvious, in the first place, that an increase in the size of the individual muscle fibers, such as occurs in hypertrophy, is not the equivalent of a corresponding increase in the number of fibers. Then, too, as the heart hypertrophies, there may be no corresponding increase in the coronary blood stream, and since the myocardium is exceedingly sensitive to changes in its blood supply, the capabilities of the larger muscle may be restricted on this account.

Associated Myocardial Changes.—It must be admitted, furthermore, that in practice hypertrophy of the heart and cardiac weakness often go hand in hand. E. Albrecht has, indeed, expressed the view that the hypertrophied heart is from the start a diseased heart. It would seem, however, that the weakness observed clinically is due not to the hypertrophy itself, but to associated myocardial changes. Thus a given cause that leads to hypertrophy through increased work may, at the same time, damage the myocardium. In rheumatic fever, for example, myocardial disease and valvular disease frequently go hand in hand. So, too, in general arteriosclerosis the heightened blood pressure is not infrequently associated with a diminution in the coronary circulation. Furthermore, according to Krehl, the hypertrophied muscle is abnormally susceptible to damage, and constitutes a place of lessened resistance in the body

where infections are apt to localize. Finally, it seems probable that a primary myocardial weakness may cause secondary hypertrophy; for just as excessive work leads to hypertrophy of the normal muscle, so may normal work, which is excessive for the weakened heart, lead to its hypertrophy.

It is evident, therefore, that although cardiac hypertrophy may under certain conditions be evidence of a strong heart muscle, it is in practice often associated with myocardial weakness.

The Work of the Heart

Since the chief cause of cardiac hypertrophy is an increase in the work of the heart, the factors which govern this work may be briefly summarized. The work of a ventricle consists partly in pumping blood into the arterial reservoir, and partly in imparting velocity to this blood. The latter factor may for practical purposes be disregarded, for, under ordinary circumstances, it makes up only about one per cent of the total work done by the ventricle. The former factor is represented by the product of the amount of blood pumped out by the ventricle and the pressure against which each portion is pumped. In man the mean arterial pressure may be roughly estimated. The determination of the cardiac output, however, is difficult and the accuracy of the various methods that have been proposed for this purpose is still under discussion. Apparently the most accurate of these methods depends upon the principle introduced by Bornstein in 1910. An inert gas is inspired, and the rate of its absorption from the pulmonary alveoli by the blood passing through the lungs forms the basis for computing the amount of blood that has passed through the lungs in a given time.

Effects of Exercise upon the Circulation

The cardiovascular changes associated with exercise are important, not alone because of their physiological interest, but also because the reaction to exercise is the simplest and the most accurate clinical test of cardiac efficiency. The degree of circulatory failure in a given patient is estimated very largely by the amount of exercise that may be taken without inducing cardiac symptoms, or by the relation that exists between the exercise and the severity of the symptoms induced.

Pulse and Blood Pressure.—During brief or moderately prolonged periods of violent exercise, such as bicycle riding, the blood pressure is raised and the heart rate is accelerated. These changes occur very promptly after the exercise is started, the increase of pulse rate slightly preceding the increase of pressure. When the exercise is stopped, there is a rapid fall of both pressure and pulse rate. The primary fall of pulse

rate usually precedes the fall of pressure; but, unlike the latter, the pulse may remain elevated for some time above its original rate and only gradually return to the normal level (Fig. 9). Variations from these typical changes in pulse rate and blood pressure depend upon the character and duration of the exercise, and upon the cardiovascular apparatus of the individual tested. Exercises of strain, as where heavy weights are lifted, cause high blood pressures with little or no increase in heart rate. Mild continued exercises, such as walking, may cause an acceleration of the pulse with no increase or even a fall in the blood pressure. In prolonged exercises there may be a diminution of the heart rate and

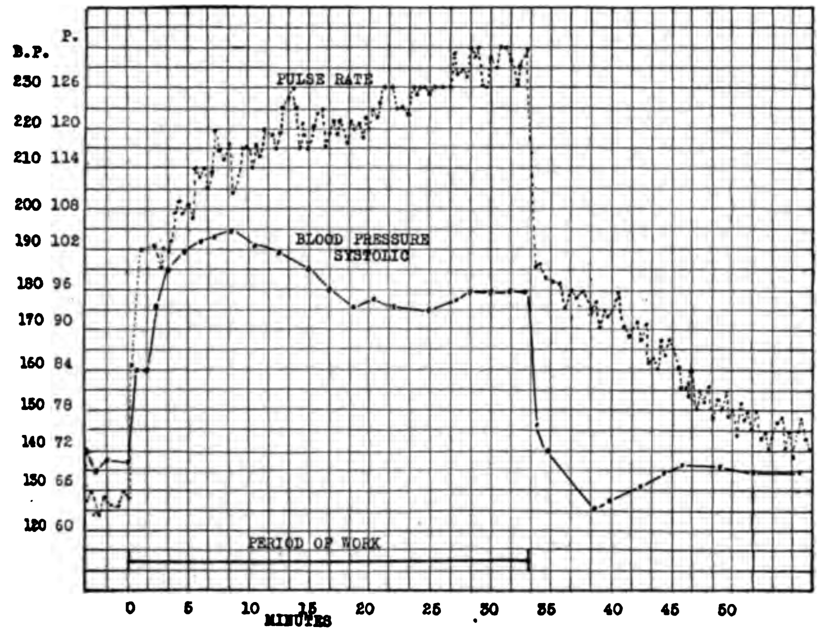


Fig. 9.—Effect of Bicycle Riding upon the Pulse Rate and the Systolic Blood Pressure. (From Bowen, Am. Jour. Physiol.)

also of the blood pressure. As a rule, however, there is during exercise an increase in the pulse rate or the blood pressure, or in both simultaneously.

Systolic Output.—The effect of exercise upon the amount of blood expelled at each ventricular systole is still under discussion. According to Henderson, the systolic output from a given heart is normally determined by the duration of diastole (page 9). An increased heart rate, such as occurs during violent exercise would, therefore, cause a lessening of the output at each systole, although the total output per minute would be increased by reason of the rapid heart rate. On the other hand, determinations of the rate of blood flow through the lungs, made

by Zuntz, Krogh and Lindhard, Boothby and others, indicate that during exercise the amount of blood expelled at each systole is increased over the normal (Fig. 10). This view is supported by the well-established fact that exercise not only raises the systolic blood pressure but increases the difference between the systolic and the diastolic blood pressures (Fig. 11). An increase in this difference, i. e., in the pulse pressure in a given individual, indicates, in a general way, that the ventricular output at each systole has been increased. The weight of evidence, therefore, favors the view that exercise not only increases the

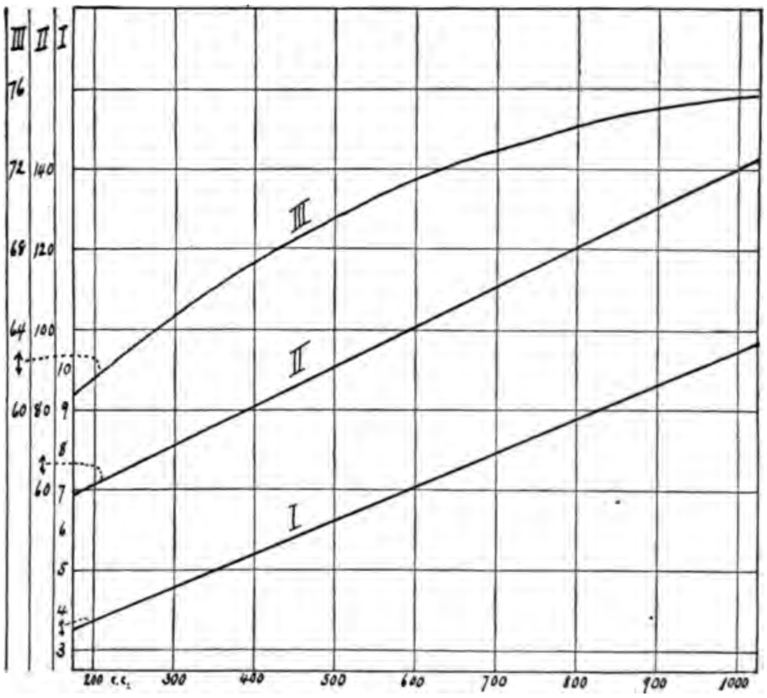


Fig. 10.—The Effect of Bicycle Riding upon the Blood Flow per Minute, the Pulse Rate and the Systolic Output at Each Beat. The Ordinates Represent (I) the Blood Flow per Minute, (II) the Pulse Rate per Minute, and (III) the Systolic Output per Minute. The Abscissa Represents the Amount of Work as Measured by the Oxygen Consumption per Minute in Cubic Centimeters. Note that with Increased Work the Pulse Rate and the Systolic Output at Each Beat Are Both Increased. (Charted from a Series of Experiments and Redrawn from Boothby, Am. Jour. Physiol.)

heart rate, but that it increases the amount of blood expelled at each systole of the ventricle.

Blood Flow.—Chauveau and Kaufmann have shown that in animals exercise causes a very marked acceleration of the blood flow through the muscles used, and the same can be easily demonstrated in man when the muscles in the forearm are exercised. During active exer-

cise the blood flow is also increased through extremities that are not used, the increase being probably due to the high blood pressure and to the rise of body temperature (Figs. 12 and 13). As to the effect of exercise upon the blood flow through the internal organs we know little; but if one accepts the marked increase in general blood flow as determined by respiratory experiments, it would seem probable that the flow is also accelerated through the abdominal and other internal organs.

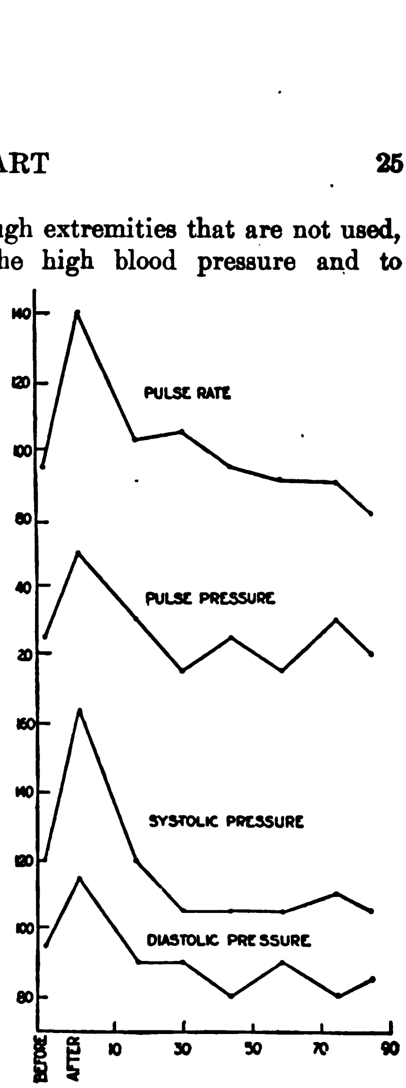


Fig. 11.—Shows the Effect of a Short Hard Run (100 Yards) upon the Pulse Rate and the Blood Pressures. Note that the Pulse Pressure Is Increased at the Time that the Pulse Is Most Rapid. (From Lowsley, Am. Jour. Physiol.)

Work of Heart.—From what has been said it is evident that muscular exertion markedly increases the work of the heart. During active exercise the mean blood pressure may be raised 50 per cent or more, while the rate of blood flow is increased to three or more times the normal. The total work of the heart which is represented by the product of these two factors would, therefore, be increased to four or more times its resting value. It is not surprising then that exercise is the great test of cardiac efficiency. Various authors have studied in detail the cardiovascular changes that occur when patients suffering from heart disease take exercise. These studies have shown that, as a rule, the rapid pulse occurring with the exercise persists in such patients for a longer time than normal after the exercise is stopped, and that, furthermore, in some patients at least, the pressure fluctuations during and after exercise differ from the normal curve. The differences, however, seem rather inconstant and they are difficult to interpret. We therefore agree with Hirschfelder in the view that cardiac insufficiency may be more readily detected and more accurately estimated by the increase of clinical symptoms during exercise, than by any method thus far advocated of following the changes in blood pressure or pulse rate.

Heart Shadow.—According to Nicolai and Zuntz, the heart shadow of normal individuals is somewhat enlarged during exercise. It is certain, however, that this enlargement, if present, disappears very promptly

when the exercise is discontinued, for numerous observations made shortly after cessation of exercise have shown that, at this time, the heart shadow is usually of normal or diminished size (Fig. 14). In patients with cardiac insufficiency, on the other hand, the heart shadow not infrequently remains enlarged for some time after the exercise has stopped. This enlargement does not appear to occur with sufficient regularity to be used as an early functional test; but it is, nevertheless, of great interest, for it indicates that the insufficient heart either dilates more readily during exercise, or does not recover from a physiological dilatation so readily as the normal. Such a failure to return to the normal size immediately after exercise is, as we have seen, comparable to the fatigue of a voluntary muscle (page 12).

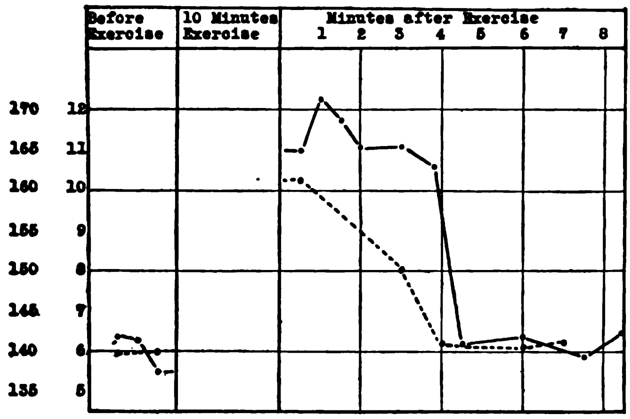


Fig. 12.—Effect of Bicycle Riding upon the Blood Flow in the Arm of Man. (Personal Observation.) Note that Immediately after the Exercise the Blood Flow (Unbroken Line) and the Systolic Blood Pressure (Broken Line) Are Both Increased and That They Fall to the Original Level at About the same Time.

Acute Dilatation.—The transition from such a mild and transient dilatation to one of a more serious and lasting character is a change in degree and not in kind. It is well known that patients suffering from heart disease may develop an acute dilatation of the ventricles as a result of unusual exercise. Such a dilatation may prove fatal, or it may incapacitate the patient for a longer or shorter time. A serious dilatation

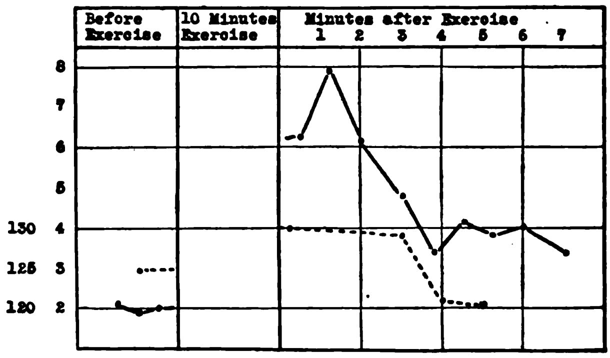


Fig. 13.—Effect of Exercise upon the Blood Flow in the Arm of Man. Compared with Fig. 12, the Main Difference Is the Slight Rise of Systolic Pressure after the Exercise and the Continuance of the Increased Blood Flow after the Systolic Pressure Has Dropped. Possibly this Late Increase Is Caused by an Elevation of Body Temperature. (See Heat Regulation.)

rarely, if ever, occurs in a normal heart in consequence of violent exercise. It is true that acute dilatation has occasionally occurred when the heart was supposed to be normal; but since myocardial weakness may escape the most careful clinical examination, there is always a possibility that such weakness was present previous to the exercise. From the theo-

A B C

Fig. 14.—Effect of Exercise upon the Size of the Heart. (A) Before Exercise, (B) After a Long Bicycle Ride. (C) Four Weeks Later. Drawn from Orthodiagraph Tracings. (From Dietlen and Moritz, Münch. med. Wochenschr.)

retical standpoint, therefore, it remains to be proved that a serious acute dilatation can be caused in a normal heart from violent exercise. From the practical standpoint, however, violent athletic contests always carry with them a certain amount of danger to the heart, for serious damage is occasionally done to a heart that appeared to be normal on clinical examination.

Exercise and Cardiac Hypertrophy

We have seen that exercise increases the work of the heart and that increased work is a cause of cardiac hypertrophy. It is but natural, therefore, to expect that when violent exercise is frequently repeated over a considerable period of time the weight of the heart muscle will increase, and that this will occur with no proportionate increase in the total body weight. Such has indeed been found to be the case. Among different species of animals the relation of heart weight to body weight varies according to the amount of exercise usually taken. The hare and the deer, for example, have relatively large hearts. In birds the heart weight may make up 2.5 per cent of the total body weight, whereas in man it ordinarily makes up only about 0.5 per cent of the body weight. There may also be considerable differences in the ratio of heart weight to body weight within a given species. The wild rabbit, for example, has a somewhat larger heart than the tame rabbit. Race horses and coursing dogs have large hearts. A dog that is allowed to run about naturally has a larger heart than one of the same litter that is kept from exercise.

Larger Heart Shadow.—Similar observations have been made with

respect to man. Henschen observed that ski runners show at autopsy relatively large hearts. On x-ray examination athletes are found to have larger heart shadows than the average, and Schieffer has shown that the German soldiers develop larger heart shadows during their military training. It is probable that this increase in the size of the cardiac shadow is due in part at least to a thickening of the heart wall.

Heart Weight and Skeletal Muscles.—It has been assumed that, in such instances, the increase in the weight of the heart was accompanied by a proportional increase in the weight of the skeletal muscles. Yet such is not necessarily the case. Külbs took two dogs of the same litter and kept one quiet in a cage while the other was made to exercise vigorously. After several months the animals were killed and the relation of the weight of the heart to the weight of the skeletal muscles was determined. It was found that the heart in the exercised animal was considerably heavier (50 per cent), even when compared with the weight of the skeletal muscles. It is evident, therefore, that severe and prolonged exercise leads to an increase in the weight of the heart, which is proportionately greater than the increase in the weight of the skeletal muscles.

Athletics and Cardiac Late Diseases.—Beyond doubt this cardiac hypertrophy enables the individual to perform greater feats of strength and more sustained feats of endurance, and to that extent it is a favorable phenomenon. Thus Barach found that the six Marathon runners who had the smallest heart shadows in his series failed to finish the race, whereas seven of seventeen runners with moderate cardiac enlargements finished. The ultimate effect of this type of cardiac hypertrophy upon the heart has not, as yet, been satisfactorily determined. While some have held that the subsequent health of famous athletes shows no deviation from the normal, others have maintained that such athletes show in later life a peculiar tendency to cardiac affections (Harlow Brooks). It is at least certain that, while the hypertrophy may be of advantage during the period of great muscular strain, it is of no advantage in later life and that it, like other forms of hypertrophy, may cause an increased susceptibility to myocardial disease.

Valvular Lesions

In every pump the orifices leading to and from the pump chamber are provided with valves which serve to direct the flow of liquid onward. In the heart, the auriculoventricular valves prevent a regurgitation from the ventricles into the auricles during systole, while the semilunar valves prevent a regurgitation from the arteries into the ventricles during diastole.

Stenosis and Leakage.—At each orifice two types of disturbance are possible. The first is due to a narrowing or stenosis of an orifice, which interferes with the free passage of blood onward. Stenoses are usually due to disease of the heart valves themselves, but occasionally, as in certain congenital lesions, the stenosis affects the arterial trunk just beyond the insertion of the valves. The second type of valvular lesion is due to a leak, which allows an escape of blood backward during the time that the valves should be closed. Since the valves are attached to a more or less yielding ring composed of muscular and membranous tissues, their proper closure is dependent in part upon the condition of this ring. Regurgitation may, therefore, be due either to disease of the valves themselves, owing to a shortening or distortion of the segments (valvular insufficiency proper), or it may be due to a widening of the musculomembranous ring to which the valves are attached, so that the latter, though themselves normal, are unable to close the widened orifice (relative insufficiency).

Aortic Stenosis

The aortic semilunar valves are thin membranous structures that normally oppose no resistance to the onward flow of blood during ventricular systole. According to Krehl, the aortic orifice is somewhat narrowed at this time by the contraction of the neighboring heart muscle, yet the blood flows smoothly past this narrowing into the wider aorta beyond without an appreciable obstruction. Disease of the semilunar valves may cause them to become stiff and rigid so that they obstruct the onward flow of blood. Furthermore, the edges of the diseased valves frequently become united at their lateral margins, thus leaving only a narrow orifice in the center.

Three Stages of Stenosis.—Experiments on animals have shown that, when the aorta is gradually obstructed just beyond the valves, the effects may be divided into three stages. Up to a certain point, constriction of the aorta produces no demonstrable effect upon the mechanism of the heart or blood vessels. The point at which this first stage of obstruction passes into the second stage, characterized by changes in the cardiac mechanism, seems to vary with the general peripheral resistance; for de Heer found that when the peripheral arterial resistance was low a relatively slight obstruction affected the cardiac mechanism, whereas when the resistance was high it required a greater constriction to produce changes. The second stage of obstruction is of particular interest to clinicians, because it causes circulatory changes that are still compatible with life. In the third or final stage of obstruction, the stenosis becomes so great that the heart can no longer maintain the circulation, and acute ventricular dilatation occurs.

Second Stage.—The second stage of aortic stenosis is characterized

by an increase in the pressure within the left ventricle during its systole. With progressing stenosis this systolic pressure may, in the dog, reach a maximum of 300 to 365 mm. of mercury. At the same time, the form of the intraventricular pressure curve changes. Instead of reaching its maximum in the earlier part of systole, the maximum is progressively shifted toward the end of systole, because the blood cannot escape freely from the contracting ventricle (Fig. 15). Furthermore, the total duration of systole tends to be increased with a lengthening of the period of systolic output. Such a lengthening is mechanically advantageous, for it enables the heart to force more blood past the obstruction. It should be remembered, however, that this prolongation of the systolic output is a late rather than an early effect of aortic obstruction.

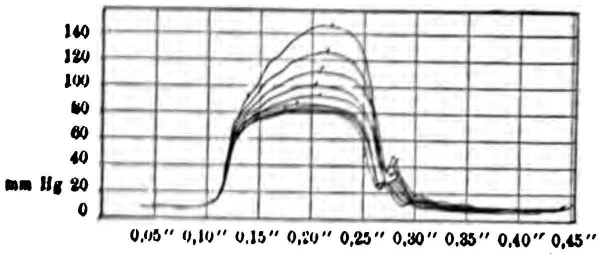


Fig. 15.—Effect of Experimental Aortic Stenosis upon the Intraventricular Pressure Curve. Note that as the Stenosis Increases the Intraventricular Pressure Rises, Particularly in the Latter Part of Systole. The Prolongation of Systole in this Experiment Is Not Marked. (From de Heer, Arch. f. Physiol.)

Dynamic Changes.—The increased pressure within the ventricle during systole leads to dynamic changes, which are similar to those produced by a heightened arterial pressure (page 6). The ventricle empties itself less completely during systole, and the residual blood left in its cavity increases the ventricular volume during diastole. At the same time, there may be but little increase in the intraventricular pressure during diastole. This dilatation of the ventricle is not, necessarily, a sign of weakness; for, as we have seen, such a dilatation enables the muscle to develop greater energy during its subsequent contraction, and this heightened pressure forces more blood past the obstruction.

Pulsus tardus. In experimental aortic stenosis the systolic output from the left ventricle is but slightly decreased during this second stage of obstruction. De Heer found a decrease of only 10 to 20 per cent. The systolic increase in the intraventricular pressure has compensated in large measure for the obstruction opposed to the onward flow of blood. The arterial blood pressure may be normal or it may be slightly reduced. The arterial pulse curve shows a rather typical change of form in marked cases of obstruction. Instead of attaining its maximum in the early part of systole, there is here, as in the curve of intraventricular pressure, a tendency to shift the maximum toward the latter part of the systolic period (pulsus tardus).

Work of Left Ventricle.—In aortic stenosis the work of the left

ventricle is increased. The pulse rate is not materially affected and the systolic output is but slightly decreased. On the other hand, there is a marked rise in the intraventricular pressure during each systole. It is to be expected, therefore, that the left ventricle will hypertrophy, and such has indeed been found to be the case.

Decompensation.—So long as compensation is good the dilatation of the left ventricle is not marked, and it is associated with but a slight increase in the intraventricular pressure during diastole. The blood flow from the lungs is not seriously retarded, and there is no marked congestion of the lungs nor any change in other parts of the heart. If the stenosis becomes excessive or if the left ventricle weakens, however, then a more marked dilatation of this cavity occurs, so that, eventually, there develops a relative insufficiency of the mitral valves along with the changes in the pulmonary circulation and in other parts of the heart that characterize that lesion. (See Mitral Insufficiency.)

Aortic Insufficiency

In aortic insufficiency a leak in the aortic valves allows blood to flow from the aorta into the left ventricle during diastole. The amount that regurgitates is difficult to estimate even in animals. Stewart held that valvular lesions, capable of causing all the characteristic changes of aortic insufficiency, allowed only a negligible regurgitation of blood. From MacCallum's experiments, however, it seems more probable that the backflow from the aorta may be considerable, and that, at times, it may even equal the inflow from the left auricle. The increased filling of the ventricle during diastole may cause but little increase in the diastolic pressure within this cavity (Wiggers), and Gerhardt has shown that in favorable cases there is no increase of the pressure in the left auricle. Apparently, therefore, the left ventricle, by virtue of a low diastolic tone, accommodates itself to the increased influx of blood from the aorta with but little increase in pressure, just as it does when the inflow from the veins is increased (page 7). There is absolutely no reason for the assumption, that the diastolic pressure in the ventricle ever approaches the diastolic pressure in the aorta.

In man also it seems probable that even marked grades of aortic insufficiency may cause but little rise in the intraventricular pressure during diastole and but little obstruction to the inflow of blood from the lungs, for it is well known that pulmonary symptoms are a relatively late manifestation in patients suffering from this valvular defect.

Dilatation of Left Ventricle.—Since the left ventricle receives and expels an increased quantity of blood at each systole, one would expect a dilatation of its cavity similar to that which occurs when the venous inflow is increased in the heart-lung preparation (page 7). Stewart as well as MacCallum found that in experimental aortic insufficiency the

ventricular volume diminished rather than increased (increased tone). In man, however, the ventricular cavity appears to be dilated even when compensation has been good. This dilatation is within limits a favorable change, for it permits the ventricle to take up more blood and to develop greater power during its subsequent systole. It is, therefore, spoken of as a compensatory dilatation.

Arterial Pressure.—In aortic insufficiency the arterial pressure during diastole falls rapidly and to an unusually low point, the cause of this fall being the regurgitation of blood into the left ventricle. The systolic pressure, on the other hand, is usually normal or even somewhat increased and in no other condition is the difference between the two so marked. This uncommonly large pulse pressure probably indicates that the systolic output from the left ventricle is markedly increased in this disease as it occurs in man.

Primary and Secondary Hypertrophy.—The work of the left ventricle in aortic insufficiency is increased, owing to the increased amount of blood that must be expelled at each systole. In consequence of this extra work, the left ventricle is always hypertrophied and often to a most marked degree. Since the extra work necessitated by aortic insufficiency falls directly upon the left ventricle, one should expect to find an hypertrophy of this chamber alone. This may indeed be found, as in one of Stadler's experiments. In most cases, however, in man as well as in the experimental insufficiency of animals, the hypertrophy, though most marked in the left ventricle, is not limited to this chamber but involves other parts of the heart. The cause for this extension is not altogether clear, but in many, if not in all cases, it is to be regarded as a secondary and not as a primary effect of the aortic lesion. We have seen that, under favorable conditions, the additional blood that enters the left ventricle during diastole causes a dilatation of this cavity, with but little increase of pressure either in this cavity or in the left auricle. In such a case, the effects of the leak are borne entirely by the left ventricle. If, however, the collection of blood in the left ventricle during diastole causes a more marked rise of diastolic pressure in this chamber, it will interfere with the free influx of blood from the left auricle and from the lungs, and will then lead to a pulmonary congestion. Furthermore, the dilatation of the left ventricle, which is almost constantly present in aortic insufficiency, may become so marked that it produces a relative insufficiency of the mitral valves, with the usual consequences for the other parts of the heart (page 35). It is obvious, therefore, that aortic insufficiency may cause secondary changes in the mechanism of the heart, which bring about an hypertrophy of other chambers than the left ventricle.

Heart Rate and the Amount of Regurgitation.—The amount of blood that regurgitates in aortic insufficiency is determined not only by

the size of the leak and the aortic pressure, but also by the duration of diastole. When the heart rate is slow, diastole is particularly lengthened, and when the heart rate is rapid, diastole is particularly shortened. It is obvious, therefore, that a fairly rapid heart rate is mechanically advantageous in aortic insufficiency, and that the increase in rate so frequently present is to be regarded as a compensatory phenomenon.

Mitral Stenosis

Lesions of the auriculoventricular valves differ from lesions of the semilunar valves, in that the cardiac chamber immediately behind the lesion possesses only a weak muscular wall. Furthermore, the auricles are not provided with valves that close during their systole, and thus prevent the blood from regurgitating into the great veins. The entrance to the great veins is normally narrowed during auricular systole by the contraction of a surrounding ring of muscle. Even under normal circumstances, however, it is doubtful if this prevents some regurgitation into

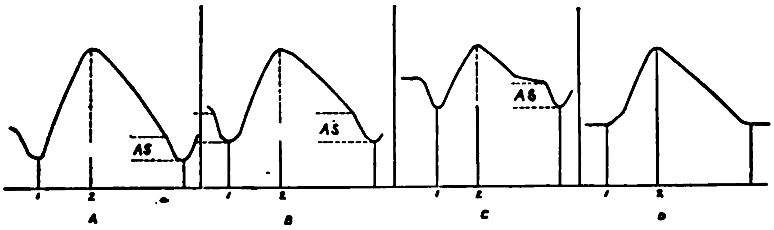


Fig. 16.—Effect of Mitral Stenosis upon Ventricular Filling. 1-2 Ventricular Systole. A Represents the Normal Relations. Auricular Systole (AS) Hardly Influences the Normal Ventricular Filling. B and C Represent Increasing Grades of Stenosis. The Auricular Contractions Play a More Important Part in Ventricular Filling. D Represents a Degree of Stenosis Comparable to B, But the Auricle Is Inactive (Auricular Fibrillation). (Modified from Hirschfelder, J. H. H. Bull.)

the veins. Under pathological conditions, and particularly when a dilatation of the auricles has caused a dilatation of the muscular rings about the veins, it is certain that considerable amounts of blood regurgitate during auricular systole.

Marginal Fusion.—In mitral stenosis the obstruction at the auriculoventricular orifice is usually produced by a fusion of the lateral margins of the valve leaflets, so that the latter become converted into a funnel-shaped structure with a round, oval or irregular hole at its end. The hole may be so small as hardly to admit a goose quill.

Distention of Left Auricle.—This stenosis obstructs the flow of blood from the left auricle to the left ventricle during ventricular diastole. In the normal heart the ventricular filling takes place most rapidly during the first part of diastole, while the amount of blood added by the auricular

contraction is relatively insignificant. In experimental mitral stenosis the filling in early diastole is particularly diminished. The amount put in by the auricular systole may be normal or increased despite the obstruction, so that it makes up a large proportion of the whole (Fig. 16). Within limits the increased distention of the auricle caused by a mitral obstruction stimulates this chamber to more powerful contractions, just as an aortic stenosis causes more powerful contractions of the left ventricle and higher intraventricular pressures during its systoles. These more powerful auricular contractions may compensate for a moderate mitral obstruction, and eventually lead to hypertrophy of the auricular muscle from increased work.

Limited Compensation; Fibrillation.—The ability of the thin-walled auricle to compensate a mitral stenosis is, however, limited. As the obstruction increases the auricle becomes more and more dilated and this dilatation eventually lessens the energy of its contractions. Furthermore, there is a marked tendency in mitral stenosis to the development of auricular fibrillation, and since the fibrillating auricle is motionless from the mechanical point of view, any compensatory power which the auricle may have possessed previously is suddenly lost when fibrillation sets in.

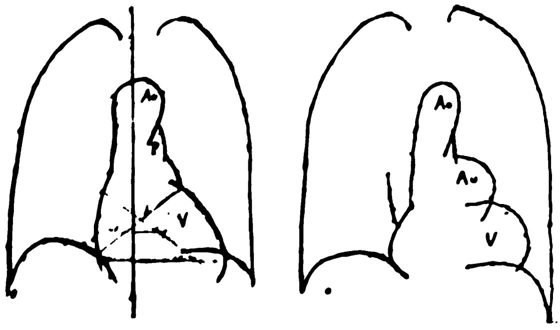


Fig. 17. Orthodiagraphs of Normal Heart Shadow (Left) and of Heart Showing a Marked Dilatation of the Left Auricle Caused by Mitral Stenosis (Right). (Kindness of Dr. Van Zwaluwenburg.)

Patients with mitral stenosis often show a very great enlargement of the left auricle. At autopsy it may even contain a pint or more of blood. During life the enlarged auricle often causes a characteristic prominence in the x ray shadow of the left border of the heart between the shadow of the ventricles and that of the pulmonary artery (Fig. 17). Pressure by the enlarged auricle may also paralyze the recurrent laryngeal nerve.

Pulmonary Engorgement.—Since no adequate valvular arrangement exists between the left auricle and the pulmonary veins, any increased pressure in the left auricle tends to be transmitted to these veins and from them to the pulmonary capillaries. For this reason, mitral stenosis gives rise early to the symptoms of pulmonary engorgement. The increase of pressure in the pulmonary circuit also leads to a rise of pressure in the pulmonary arteries. The second pulmonic sound becomes accentuated, and the right ventricle in pumping against this increased pressure does more work and becomes hypertrophied. The rise of pressure in the

pulmonary circuit which is maintained by the extra work of the right ventricle, assists in forcing blood past the mitral obstruction and is, therefore, a compensatory process, for it aids in maintaining a normal rate of blood flow. Eventually, however, the right ventricle may weaken and dilate, so that blood collects in the systemic veins with the symptoms and signs of a general passive congestion.

Reduced General Circulation.—Mitral stenosis tends to reduce the circulation as a whole. The pulse is often remarkably small. At autopsy the left ventricle may be normal in size or it may be atrophied. This atrophy is an atrophy of disuse, and is due to the decreased amount of blood that is pumped by the left ventricle.

Mitral Insufficiency

Leaks at the mitral orifice cause a regurgitation of blood into the left auricle during ventricular systole. Such leaks may be caused by *diseases of the valves themselves.* The vegetations that appear on the valves as a result of endocarditis may interfere with their close apposition, and ulcerations may cause valvular defects. More important, however, are the changes secondary to inflammation which cause shrinkage and deformities of the segments. Mitral leaks may also be due to changes in the muscular ring to which the valves are attached, or to changes in their cordæ tendineæ. The apposition of the valvular segments is assisted normally by the systolic contraction of the surrounding ring of muscle, while the papillary muscles with their cordæ tendineæ prevent the valves from being pushed back too far into the auricular chamber. When the heart muscle is weakened, the imperfect contractions of the mitral ring or of the papillary muscles may allow a leak to occur even though the valves themselves are normal. When the valves are diseased, a muscular insufficiency still further increases the leak. A dilatation of the left ventricle, such as may occur from myocardial weakness, from aortic disease, or from chronic arterial hypertension, is frequently associated with a dilatation of the muscular ring supporting the mitral valve. This gives rise to the type of mitral insufficiency which is spoken of as a *relative or muscular insufficiency.*

Effect on Left Ventricle.—So far as the left ventricle is concerned, the effects of mitral insufficiency are very similar to the effects produced when the ventricle must pump excessive quantities of blood (page 7). The blood that is regurgitated into the left auricle enters the ventricle again at the next diastole together with the blood that has come through the lungs. The left ventricle is more distended during diastole, and it contracts more energetically at the next systole with the expulsion of blood both into the aorta and into the left auricle. By increasing its stroke, the left ventricle may deliver the requisite amount of blood to the aorta

in spite of the mitral leak, and thus maintain a satisfactory circulation in the systemic vessels. The extra amount of blood pumped at each stroke, however, necessitates an increased amount of work on the part of the left ventricle, and this causes the hypertrophy that is regularly found at autopsy. The cavity of the left ventricle tends to become dilated on account of the increased amounts of blood that enter it at each diastole. In its earlier stages, this dilatation is of a compensatory character, for it enables the ventricle to do the extra work demanded of it.

Auricular Pressure.—The milder grades of mitral insufficiency may cause but a slight and transient increase in the intra-auricular pressure. The blood lost by the leak is returned to the ventricle at the next systole without a serious obstruction to the flow of blood through the pulmonary circuit. When the insufficiency is more marked, however, the pressure in the left auricle is continuously elevated, and the effects produced upon the left auricle, the pulmonary circuit and the right ventricle are in every way similar to those produced by mitral stenosis. The left auricle, at first, becomes moderately distended and hypertrophied but, finally, markedly dilated and weak. Auricular fibrillation is common. The pressure in the pulmonary circuit becomes increased with accentuation of the second pulmonic sound, the work of the right ventricle is increased, and eventually hypertrophy, weakness, and dilatation of this chamber occur. As in mitral stenosis the increased pulmonary pressure is, to a certain extent, a compensatory phenomenon, for it increases the filling of the left ventricle during diastole, and so increases the amount of blood that may be expelled from this cavity.

Valvular Lesions of the Right Heart

Isolated valvular disease of the right side of the heart is relatively uncommon, for infectious processes localize more commonly on the valves of the left side. The effect of right-sided lesions upon the size of the cavities and the hypertrophy of the muscle is very similar to the effects produced by similar left-sided lesions; diseases of the pulmonary valves being comparable to aortic diseases, and diseases of the tricuspid valves being comparable to mitral diseases.

Systemic Arterial and Venous Pressure.—The right side of the heart differs, however, from the left side in that a rise of pressure in the systemic veins leads to no corresponding rise in the systemic arterial pressure. We have seen that in mitral disease the rise of pulmonary pressure is sustained by the increased work of the right ventricle and that this compensates to a certain degree for the unfavorable effects of the valvular defect. This mechanism finds no analogy in tricuspid disease, for there is here no rise in the systemic arterial pressure and no hypertrophy of the left ventricle.

Tricuspid Insufficiency.—Tricuspid insufficiency is most frequently of the relative type, being due to a dilatation or weakness of the right ventricle rather than to a disease of the valves. Clinically it is usually associated with disturbances on the left side of the heart, or with obstructions to the flow of blood through the lungs. The blood thrown back into the right auricle during ventricular systole tends to increase the pressure in this cavity and in the systemic veins. It was formerly held that such a regurgitation during systole would be immediately evident upon the venous pulse, and that instead of the normal fall in the venous curve during systole there would be a rise, producing the so-called positive venous pulse. We now know, however, that the normal fall in the venous pulse during ventricular systole is due in large measure to auricular diastole, and that, so long as the right auricle is contracting normally, this fall may occur even though tricuspid insufficiency be present. Only in marked cases of tricuspid insufficiency with failing contraction of the auricle is the positive venous pulse to be expected. We have learned, furthermore, that a positive venous pulse is frequently produced by conditions other than a tricuspid insufficiency, and particularly by a simultaneous contraction of auricles and ventricles (Fig. 32), as well as by an absence of normal auricular contractions, such as occurs in auricular fibrillations (Fig. 41). Except in marked instances of tricuspid regurgitation, therefore, the form of the venous pulse is of uncertain value as a diagnostic sign, and it must always be interpreted with due regard to the condition of the auricles.

Compensation. Effect on Liver.—The heightened venous pressure in tricuspid regurgitation causes a more complete filling of the right ventricle with increased stroke and hypertrophy, just as occurs on the left side of heart during mitral regurgitation. By this means a certain degree of compensation is possible. The circulation may be maintained and the venous pressure may be kept from any considerable rise. It is obvious, however, that with increasing insufficiency the systemic venous pressure will rise, and that the usual signs of passive congestion of the internal organs will develop. The enlarged, tender, and later cirrhotic liver is familiar evidence of insufficiency of the right side of the heart. This enlargement of the liver may be due, in part, to the close proximity of the hepatic vein to the right auricle, but there seem to be, in addition, certain physiological differences between the liver and the other internal organs when all are subjected to a rising venous pressure. Thus Thacher found that when the venous flow to the right auricle was suddenly obstructed the volume of the liver and brain increased, whereas there was a reduction in the volume of the kidney, the spleen, the small intestines and the extremities. This reduction was due partly to a diminution in the arterial inflow, and partly to a constriction of the local blood vessels. Similar changes probably occur in any acute insufficiency of the right

heart. The liver, therefore, seems to act as a reservoir which takes up the excessive quantity of venous blood, whenever the systemic venous pressure is suddenly increased.

WEIGHT OF THE CARDIAC CHAMBERS.—The effects of an isolated tricuspid insufficiency upon the weight of the various cardiac chambers has been studied experimentally by Stadler. He found that the right ventricle, like the left in mitral insufficiency, is regularly hypertrophied in consequence of this lesion. The left ventricle in some animals was normal, in others it was diminished in weight. This diminution, like that occasionally seen in mitral stenosis, is due to relative disuse, owing to a reduction in the amount of blood coming to it.

Congenital Heart Lesions

Of the commoner congenital lesions, compatible with life and growth, a stenosis at or just beyond the pulmonary orifice leads to changes analogous to those that have been described in aortic stenosis. The other common lesions: patent foramen ovale, open ventricular septum, and patent ductus arteriosus, are all characterized by the fact that an opportunity is afforded for blood to pass freely between the systemic and the pulmonic circulations. With an open foramen ovale, relatively little blood ordinarily crosses the septum, for there is probably no great difference of pressure in the two auricles. Unless the opening is very wide, therefore, or unless congestion occurs on one side or other of the septum (serious pulmonary disease), the lesion is usually not serious. In open ventricular septum or patent ductus arteriosus, on the other hand, there is a marked difference in pressure on the two sides of the opening. The pressure in the aorta is normally two or three times that in the pulmonary artery, and in open ductus arteriosus a continuous current of blood passes from the aorta to the pulmonary artery. The pressure in the latter is increased, the second pulmonic sound is accentuated, and the right ventricle becomes hypertrophied and eventually dilated. The loss of blood from the aorta may lead to a low diastolic pressure. When there is an opening between the two ventricles, blood passes directly from the left to the right ventricle and the latter becomes hypertrophied and dilated.

Combined Valvular Lesions

Valvular disease frequently involves more than one valve, and even when a single valve is affected there is often present both an insufficiency and a stenosis. Furthermore, any valvular lesion is apt to be complicated by a relative insufficiency at the mitral or tricuspid orifice, owing to ventricular dilatation or myocardial disease.

Summation of Individual Effects.—The effect of such combinations is

in general a summation of the individual effects. Yet certain combinations appear to be relatively favorable, whereas others are relatively unfavorable. The combination of aortic stenosis with mitral insufficiency, for example, is an unfavorable combination, for the heightened intraventricular pressure necessary to force sufficient blood through the narrowed aortic orifice increases the mitral leak. On the other hand, the combination of an aortic stenosis and a mitral stenosis is relatively favorable, for each lesion during its period of compensation does not interfere with the other.

Relatively Favorable Effects.—The combination in a single valve of stenosis and insufficiency of a given degree is, in general, more serious than when either one of these lesions is alone present. On the other hand, as a valvular disease progresses the edges of the leaflets may become more and more adherent to one another. The increase in stenosis that results may be associated with a diminution in a previous insufficiency. Under such circumstances the circulatory conditions may improve as the stenosis develops. Such an improvement, however, is due not to any beneficial mechanical effect of the combination, but to a diminution in the leak.

We have seen that, when the ventricle becomes very much dilated, a relative insufficiency may develop at its auriculoventricular orifice. The regurgitation, thus produced, may at times be of distinct benefit in that it relieves the ventricle of a certain amount of blood, and lessens, for the time being, the danger of serious dilatation. Particularly under conditions of unusual and temporary strain, such a leak may prove a safety valve which relieves the ventricle of imminent danger. Somewhat similarly the development of a relative tricuspid insufficiency, in patients with serious pulmonary congestion, may relieve the pulmonary congestion by allowing more blood to collect in the systemic veins. Such a change is unfavorable in that it reduces the total blood flow, yet it may relieve certain symptoms due to the pulmonary congestion, and for the time at least prove beneficial.

Effect of Some Extraneous Factors Upon the Heart

Arterial Hypertension

An increase in the systemic blood pressure may be due either to an increased output from the heart, or to an increased resistance in the peripheral vessels. The former, as we have seen, is the main cause of the rise of blood pressure that accompanies muscular exertion. In most pathological conditions, however, arterial hypertension is due to an increase in the peripheral resistance caused by a lessened diameter of the finer arterioles.

Acute.—Transient rises of blood pressure may occur in association with emotional excitement, acute asphyxia, acute cerebral compression, lead colic and angina pectoris. Pal has grouped such temporary hypertensions together and has called them *general vascular crises.* The effect produced by an acute rise of blood pressure upon the normal heart is comparable to that produced when the pressure, against which the left ventricle must pump, is suddenly raised in Starling's heart-lung preparation. Such a rise, as we have seen, causes a moderate increase in the size of the left ventricle which enables the ventricle to develop more energy, and to deliver a normal or nearly normal quantity of blood into the aorta despite the heightened blood pressure. It is possible, as Hirschfelder believes, that in the intact animal the heightened blood pressure may at times be associated with an increased ventricular tone, so that no dilatation whatever occurs. At any rate, the physiological dilatation, if present, is not extreme, and the normal heart may pump against enormous rises of blood pressure without signs of failure and without an appreciable rise of pressure in the pulmonary circuit. If, however, the ventricular muscle be already weakened by disease, an acute rise of blood pressure may be dangerous. The weakened heart is already somewhat dilated, and its ability to overcome a rise in arterial resistance is distinctly less than the normal. A sudden increase of resistance, due to vascular spasm, may so increase the strain on the left ventricle, as to lead to an acute and extreme dilatation with relative mitral insufficiency, pulmonary congestion, and possibly even death.

Chronic.—Chronic arterial hypertension is probably due to an increased resistance in the smaller arterioles throughout the body (page 107). It leads to an increase in the work of the left ventricle, and this, in turn, causes an hypertrophy of the ventricular muscle. At autopsy such ventricles always weigh more than the normal, and the ventricular cavity is often dilated. During life the aortic second sound is usually loud, and the ventricular enlargement is readily demonstrated by the usual methods of physical and x-ray examination. According to Pässler, hypertrophy of the right ventricle in patients with chronic arterial hypertension is a secondary phenomenon and is not present in those who have shown no evidence of cardiac insufficiency. He believes that in the earlier stages of chronic hypertension the left ventricle alone is affected. A weakening of its muscle or the development of a relative mitral insufficiency leads to a secondary congestion of the lungs and this in turn increases the work of the right ventricle and causes its hypertrophy.

Pulmonary Disease

We have seen that a passive congestion of the pulmonary vessels, induced by mitral disease or by weakness of the left ventricle, leads to an

increased pressure in the pulmonary artery, and eventually to an hypertrophy of the right ventricle, which may in turn lead to dilatation.

Obstruction of Circuit.—The effect of obstructing portions of the pulmonary circuit has been studied experimentally by numerous observers. These studies have shown that it is possible to obstruct a large part of the pulmonary circulation, even up to three-fourths, without affecting the carotid pressure. A large part may also be obstructed without diminishing the output from the left heart, and without increasing the pressure in the systemic veins. It is evident, therefore, that a normal circulation may be maintained even though a considerable portion of the pulmonary vessels is thrown out of function. How is this accomplished? Evidently it must be done either by a rise of pressure in the pulmonary artery, which forces the normal quantity of blood through the reduced pulmonary circuit, or else there is a dilatation of the remaining pulmonary vessels. Both factors play a part; but since the rise of pressure in the pulmonary artery is not marked during such obstructions, the latter factor seems to be the more important, and one must conclude that the vessels in the lungs readily yield under slight increases of pressure.

Pulmonary Distention.—The circulation through the lungs is also influenced by the degree to which the lungs themselves are distended. The contention that a collapsed lung permits a more rapid flow of blood seems incorrect (page 390). It would appear rather that the normally distended, or slightly overdistended lung, offers less resistance to the flow of blood. Under pathological conditions pulmonary collapse is often associated with increased external pressure on the affected lung, and distention is often accompanied by a further lowering of the negative pressure to which the lung is normally subjected. These changes in external pressure likewise favor a more rapid blood flow through a distended, as compared with a collapsed, lung.

Increased Work of Right Heart.—Experimental studies as well as clinical experience indicate that the work of the right heart is increased only by extensive pulmonary disease. Patients who die of pulmonary tuberculosis usually show some hypertrophy of the right ventricle. According to Wideroe, this hypertrophy is more marked in elderly patients, in those who have long suffered from the disease and in those with extensive lesions. In this connection it may be pointed out, that the size of the heart shadow in tuberculous individuals as determined during life by the x-ray is, on the average, smaller than the normal heart shadow. The cause of this discrepancy between x-ray determinations and autopsy records is not evident; but it may depend either upon the low blood pressure, frequently seen in such patients, or upon an increased tone of the heart muscle, either of which might cause the ventricles to expel their contents more perfectly than usual.

Pulmonary Emphysema.—In pulmonary emphysema the loss of capil-

laries in the affected portions of the lungs together with the sclerosis of the pulmonary arterioles that may be present lead to a reduction in the total cross-section of the pulmonary circuit. In the earlier stages of the disease, this may be neutralized to some extent by the increased size of the thoracic cavity which increases the size of the lungs, and thus probably lessens the resistance in the remaining vessels. In such patients, the size of the heart shadow is often normal or even less than the normal. Eventually, however, the loss or narrowing of blood vessels together with the effects of continued cough lead to an hypertrophy of the right ventricle. The advanced stages of emphysema are not infrequently complicated by a serious insufficiency of the right heart with a rise of pressure in the systemic veins.

VARYING INTRATHORACIC PRESSURE.—Obstructions to the free transit of air through the air passages, such as occur in bronchial asthma and tracheal or laryngeal stenosis, influence the work of the heart. It is obvious that the normal respiratory variations of intrathoracic pressure will be markedly increased, when there is an obstruction to the free entrance and exit of air. These variations of pressure normally cause changes in the size of the capillaries and veins within the thorax, and changes in the blood flow to the heart. If these variations in blood flow be increased by stenosis of the respiratory passages, the heart is called upon to accommodate itself to unusually wide fluctuations in the inflow of blood during each phase of respiration. During coughing there is a sudden and transient increase in the intrathoracic pressure, which is followed by a sudden fall. Such sudden changes in intrathoracic pressure will likewise tax the heart and, particularly, the right ventricle. It seems probable, therefore, that the hypertrophy of the heart and particularly of the right ventricle that has been observed in patients suffering from chronic bronchitis and related conditions, is due in part to these sudden and unusual fluctuations in the intrathoracic pressure.

Plethora, Anemia, etc.

The older pathologists believed that plethora, or an increased amount of blood in the body, played an important part in producing cardiac hypertrophy. It seems not improbable that many of these supposedly plethoric individuals were, in reality, suffering from chronic arterial hypertension, and that the latter was the immediate cause of the hypertrophy observed. An increased amount of blood in the body does not necessarily lead either to hypertension or to an increased output from the heart, for the increase may well be taken up by a proportionate increase in the size of the blood vessels. Modern determinations have shown that the amount of blood in the body is usually increased in certain conditions, and particularly in polycythemia and in anemias of the chlorotic type (see Plethora). Yet

there seems to be no unusual hypertrophy of the heart in these patients, provided there is not an associated increase in arterial blood pressure. Nor did Hess find any cardiac hypertrophy, when plethora was artificially produced in animals by repeated injections of blood from other animals of the same species.

Anemia and Rate of Circulation.—According to determinations of the blood flow made by Plesch, the rate of circulation is markedly increased in the severe anemias, and this increase is believed to be a compensatory measure which enables such patients to be relatively comfortable, in spite of their very low percentages of hemoglobin (page 369). As a rule, however, such patients show no marked hypertrophy of the heart, such as one would expect as a result of the calculated flows. The effect of severe anemia upon the cardiac mechanism is, therefore, rather uncertain at the present time.

"Beer Heart."—It has long been known that the heavy beer drinkers of Munich not infrequently have unusually large hearts. This "beer heart" has been variously attributed to the amount of liquid taken, to the alcohol, or to the heavy work which these men often do. Recent observations in Fr. Müller's clinic indicate that a chronic hypertension is very common in these individuals, and it seems probable that this is the immediate cause of their cardiac hypertrophy.

Compensation and Decompensation

Compensation

A heart lesion is said to be compensated when the results of the mechanical changes produced by disease are more or less overcome, and the circulation is maintained in a normal or nearly normal manner. We have seen that compensation is accomplished by a variety of agencies, chief among which are an hypertrophy of the muscle and a "compensatory" dilatation of the cardiac chambers. These lead to an increase in the ventricular output, or to an increase in the energy of the ventricular contractions. It is usually assumed that the rate of blood flow during compensation is normal; but since this rate is not readily determined in man, the *ordinary criterion of a good compensation is an absence of cardiac symptoms.* The degree of compensation varies. When an individual is able to pursue the ordinary affairs of life in spite of his heart lesion, compensation is good. When his activities are only somewhat restricted, compensation is partial. Finally, when his activities are seriously interfered with or must be given up entirely, compensation has failed.

Compensated Circulation Not Normal.—Even though compensation be good and the normal quantity of blood be supplied to the body, nevertheless the compensated circulation is not a normal circulation. The very

changes necessary to maintain a normal flow of blood may carry with them certain disadvantages and certain dangers. We have seen that cardiac lesions cause an increase in the size of certain parts of the heart owing to dilatation and hypertrophy. This increase in size lessens the available lung space in the thoracic cavity; and while such a limitation is not ordinarily serious it may, in extreme cases, interfere with respiration. Of greater importance is the fact that mitral lesions usually cause an increased pressure in the pulmonary circuit. This serves the useful purpose of forcing more blood into the left ventricle. On the other hand, the collection of blood in the lungs is not without its disadvantages. It causes the anatomical changes characteristic of passive pulmonary congestion, increases the tendency to pulmonary infection, may cause microscopic or gross hemorrhages, and probably plays a part in the etiology of the dyspnea that occurs so early in mitral valve disease. In tricuspid disease a similar congestion of the systemic veins occurs, even though a normal amount of blood is being pumped by the heart. In aortic insufficiency the wide fluctuations in the arterial blood pressure at each beat cause violent pulsations of the arteries, and the associated throbbing sensations may become very distressing. These violent pulsations are also the probable cause of the arterial widening and the anatomical changes in the arterial walls, that have been repeatedly noted in connection with aortic insufficiency. It is evident, therefore, that in valvular as well as in muscular disease of the heart the average blood flow may be normal and yet changes of more or less importance have taken place in different parts of the circulatory apparatus.

Causes of Broken Compensation

Only occasionally is there an abrupt failure in a previously normal circulation. The rupture of an aortic valve, the lodgment of an embolus in a coronary artery, the acute dilatation of an apparently normal heart during violent exercise, are examples of such sudden failure. As a rule, failure occurs in hearts which have shown previous evidence of disease, and in which a certain degree of compensation has been established. What are the causes of such a failure?

Progressive Lesions.—Compensation may fail because the original lesion is a progressive one, and the demands made by this lesion ultimately exceed the compensatory powers of the circulatory apparatus. In stenosis of the mitral valve, for example, the orifice may become so small that, in spite of all compensatory measures, sufficient blood cannot be forced past the narrowed orifice. Similarly an aortic leak may become so great that the greatest hypertrophy and dilatation, of which the left ventricle is capable, ultimately fail to maintain a satisfactory circulation.

Extraneous Demands; Muscular Exercise.—Compensation may also fail because increased demands of an extraneous character are made upon

the heart. A rise of blood pressure due to a widespread vascular constriction may overtax a weakened ventricle. In aortic insufficiency such a rise not only increases the resistance during the ventricular systole, but it increases the amount of blood that regurgitates during diastole. A rise of arterial pressure is particularly disadvantageous in this lesion. Of all extraneous demands made upon the heart, however, the most important is muscular exercise. During severe exercise the minute output of the heart is always increased and, according to the determinations of Krogh and Lindhard, it may even be five or more times the normal minimum. The blood pressure is also elevated. Both these factors increase the work of the heart. It is not surprising, therefore, that diseased hearts, which maintain an adequate circulation for the resting body, are unequal to the task of maintaining the increased circulation that is necessary during exercise. When the exercise ceases, the heart may again be capable of doing the work required of it, but the frequent repetition of excessive demands exercises an unfavorable influence on cardiac compensation. Conversely, if exercise be so restricted that the limits of compensation are never overstepped, time is given for the adjustments, and, particularly, for the hypertrophy requisite for compensation. For this reason rest in bed plays an important part in the treatment of every cardiac insufficiency. Occasionally muscular exertion so far exceeds the limits of accommodation, that a serious and even irreparable damage is done to the heart within a brief period of time.

Disease of the Heart Muscle.—A most important cause of cardiac decompensation is disease of the heart muscle. A progressive myocarditis or an advancing sclerosis of the coronary arteries ultimately reduces the strength of the muscle and causes insufficiency. Disease of the heart muscle is frequently due to an acute infection, and it is by no means uncommon to encounter patients whose symptoms of decompensation date from an apparently insignificant "cold." The changes induced by an infection may be of a chronic, progressive character, or they may be acute and terminate in recovery. Of great importance is the fact, that those who have once suffered from acute myocarditis as a result of chronic tonsillar disease are liable to further attacks of similar origin; and, for this reason, the removal of the primary source of infection becomes of paramount importance in the prophylactic treatment of such patients.

Dangers of Hypertrophy.—Hypertrophy of the heart seems to carry with it the danger of failure. In most cases, this failure is attributable to the factors just discussed, and possibly to some special susceptibility of the hypertrophied muscle toward infection. The view of certain observers that hypertrophy in itself leads, eventually, to weakness has been referred to elsewhere (page 21).

Changes in Cardiac Rhythms.—Finally, compensation may be disturbed by changes in the cardiac rhythm. Premature contractions with a

relatively small output of blood place an extra strain on the heart at the next heart beat. If these recur frequently, or in succession, they may lead to insufficiency in a heart that is already working near its limit. In other disturbances of rhythm, the auricles and ventricles contract simultaneously, and the auricles being unable to throw blood into the ventricles during their systole, empty a part of their contents back into the veins. It is obvious that this mechanism is an undesirable one. Most important of all the irregularities, however, is auricular fibrillation. In this arrhythmia the auricles are, from the mechanical standpoint, practically motionless. We have seen that in mitral stenosis the increased auricular contractions may play a part in forcing blood past a moderate obstruction, and that when fibrillation sets in this auricular compensation is lost. Auricular fibrillation is most serious, however, because it usually causes a rapid and very irregular ventricular rhythm. Many of the smaller ventricular systoles may fail to expel sufficient blood to cause a palpable radial pulse, the energy of ventricular contraction being wasted in simply raising the intraventricular pressure. It is not surprising, therefore, that the onset of auricular fibrillation frequently coincides with an aggravation of cardiac symptoms, and that the patient, who had formerly been comfortable, suddenly becomes breathless on exertion, and develops other evidences of cardiac insufficiency.

Effects of Decompensation

The manifestations of cardiac decompensation depend, in the first place, upon a diminution in the minute output from the heart and a general slowing of the blood stream throughout the body. Owing to this slowing, the supply of oxygen and of food material to the tissues, and the removal of carbon dioxid and other waste products from them, will be interfered with. The character of the nutritional changes that follow is, however, but imperfectly understood. The manifestations of cardiac insufficiency depend, in the second place, upon an abnormal distribution of blood. There is a collection of blood in the veins and a passive congestion of various organs. When the left side of the heart weakens, this congestion is most marked in the lungs, and when the right side of the heart weakens, it is most marked in the systemic veins and organs.

While the manifestations of cardiac insufficiency, such as the dyspnea, the swollen liver, the albuminuria, the edema and the gastro-intestinal disturbances, are doubtlessly due to these two factors, lessened blood flow and venous congestion, the exact mechanism of their production, in each case, is more or less obscure, and it will be discussed under the appropriate headings.

Dilatation of Heart Cavities.—Decompensation is usually associated with the dilatation of one or more cavities of the heart. Any rise of venous pressure increases the diastolic filling of the corresponding auricle

and ventricle. The chambers thus affected contract more powerfully at first, and thus tend to pump more blood from the venous to the arterial side of the vascular system. Eventually, however, the energy of the contractions lessens, and this favors further dilatation of the cardiac chambers.

Systemic Arterial Pressure.—It might be assumed that a lessened output from the left ventricle would cause a fall of the systemic arterial pressure in all cases of broken compensation. Yet such is not the fact, and, even with advanced decompensation, the arterial pressure is usually maintained at a normal or even a heightened level. Furthermore, when compensation is reëstablished by rest and the use of digitalis, the blood pressure may fall to a lower level than that maintained during decompensation. Since the systolic output from the heart during decompensation is diminished, the blood pressure must be maintained at or above the normal level by an increase in the constriction of the peripheral arterioles, which thus compensate or overcompensate for the reduced cardiac output. Sahli has designated this condition as a "high pressure stasis." According to Lang and Manswetowa, the increase in the blood pressure during decompensation is particularly marked in those suffering from mitral disease or from pulmonary emphysema. Possibly, as these authors suggest, this may be because the left ventricle is but little affected in these conditions. Possibly, also, it depends upon the more marked cyanosis, which often accompanies these conditions, and which may stimulate the vasomotor center and so increase the peripheral resistance.

Disturbance of Cardiac Rate and Rhythm

Fundamental Properties of the Heart Muscle

The heart muscle possesses certain fundamental properties which determine the rhythm and force of the cardiac contractions. Like living tissue in general, it is responsive to external stimuli, its most manifest response to such stimuli being a contraction. *Irritability* and *contractibility* are, therefore, two of the fundamental properties of the heart muscle. The heart muscle not only contracts in response to external stimuli, but it has, in addition, the property of *initiating spontaneous beats.* The exact mechanism that initiates such beats is not understood, but it is usually assumed that, after each cardiac contraction, there is a gradual accumulation of certain unstable compounds in the heart muscle which finally reaches a point where these suddenly decompose, and, in doing so, initiate a cardiac contraction. By virtue of the fourth property of the heart muscle, its *conductivity,* contractions which have been initiated in one region of the heart are conducted to adjacent regions. An impulse wher-

ever started tends, therefore, to produce a systole of the entire heart. The final property of the heart muscle, its *tone*, has already been discussed. (See Dynamics of the Heart Muscle.)

The Refractory Period

Immediately after a cardiac contraction there is a marked depression of certain functions of the muscle. At this time powerful external stimuli produce no effect. The irritability of the muscle rapidly increases, however, so that contractions can soon be produced: first by strong, and then by weaker stimuli. Conduction through the cardiac tissues is also abolished immediately after a contraction, and the conduction improves from zero to the normal during the early portion of the diastolic pause. The refractory period plays an important part in the analysis of certain cardiac arrhythmias, for the reason that, at this time, stimuli are conducted poorly or not at all, or having reached a cardiac chamber that has just contracted, they may produce no systole.

The Pacemaker of the Heart

Although any portion of the heart muscle is inherently capable of initiating contractions, the pace of the whole organ is ordinarily governed by impulses that arise from a single region, where the automatic rhythm is more rapid than in any other part of the heart muscle. Contractions initiated by this pacemaker spread to all parts of the heart and discharge the unstable compounds that are collecting elsewhere. The automatic rhythms of outside regions, therefore, do not become evident under normal conditions. If, however, by reason of impaired conduction, the entire heart is not discharged with each beat, an opportunity is afforded for impulses to be built up in the undischarged regions. This happens, for example, in the ventricles when the conduction of impulses from the auricles is interrupted. The function of pacemaker may also pass from the normal to an abnormal site, whenever the inherent automatic rate of the latter exceeds the automatic rate of the former. This may occur because the formation of beats in the normal pacemaker is slowed, or because the formation of beats elsewhere is accelerated, or because a combination of these conditions exists.

Sinus Node.—The pace of the heart is controlled normally by impulses that arise in the region of the sulcus terminalis, at the junction of the superior vena cava and the right auricle (Fig. 18). In this region there lies a club-shaped node of specialized tissue, the so-called sinus node, which differs from adjacent portions of the heart muscle in that the fibers are smaller and less definitely striated while their nuclei are more elongated. This node contains numerous nerve cells. It has been

definitely proved that the cardiac rhythm normally takes its origin in this node, and usually at about the level of its widest portion. The application of cold or of heat to this region causes a slowing or acceleration of the heart rate, whereas applications to other regions are for the most part without effect (Ganter and Zahn). Furthermore, electrocardiographic studies have shown that electric negativity, which always accompanies muscular contractions, usually appears in the widest portion of the sinus node before it appears in other parts of the auricles.

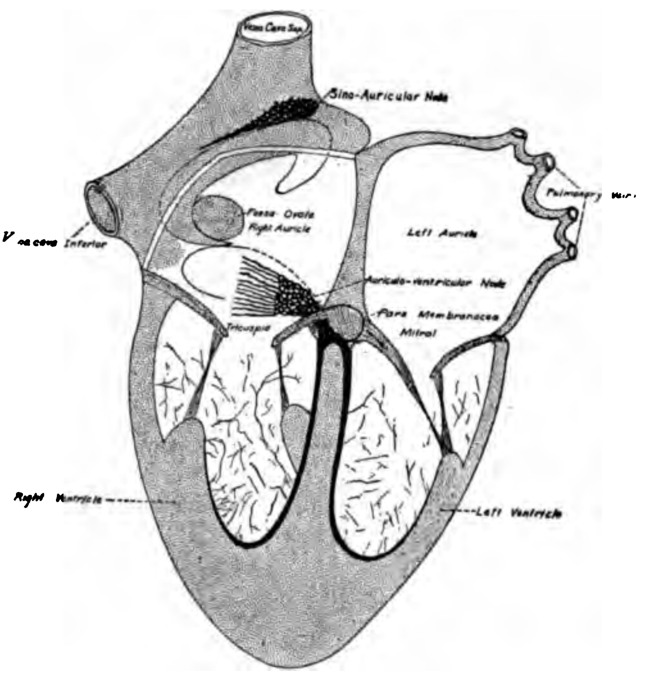


Fig. 18.—Diagram of the Specialized Heart Tissues. The Pace of the Heart Is Normally Determined by the Sino-auricular Node. Conduction from the Auricles to the Ventricles Occurs Through the Auriculoventricular Node. The Ventricular Prolongation from the Latter (His Bundle) Divides Into Two Main Branches which Proceed Toward the Apex and Give off Branches to the Inner Surface of the Ventricular Walls. (Redrawn after Koch, Ztschr. f. exp. Path. u. Therap.)

Conduction Paths

The impulses which originate in the sinus node travel to the auricular muscle and to the auricular terminations of the specialized tissues which connect the auricles with the ventricles. Whether a definite path is traversed between the sinus node and the auriculoventricular conduction system, and if so, what that path is, has not been established.

Tawara's Node and His Bundle.—The conduction system between the auricles and ventricles consists of a node of specialized tissue, the auriculoventricular node of Tawara, together with extensions from this node into the auricles and into the ventricles. The latter extension constitutes the bundle of His, and it is the sole functional connection between the auricles and ventricles. This bundle enters the interventricular septum and there divides into right and left branches, which supply the right and left ventricles respectively. Each of these main subdivisions proceeds toward

the apex of the heart and gives off its first large branches to the papillary muscles. The ultimate ramifications of the His bundle consist of the well-known Purkinje fibers, that lie on the inner surface of the ventricular muscle.

Heart Muscle and Nerves

Myogenic and Neurogenic Theories.—The heart, even though separated from all extrinsic nerves, continues to beat in a normal manner, and stripes of cardiac muscle, if placed under proper conditions, execute rhythmic contractions. Whether in mammals this automatic ~~cavity~~ activity of the heart resides solely in its muscular fibers (myogenic theory), or whether it depends in part or in whole upon nerve cells that lie imbedded in the muscle (neurogenic theory), is still a subject of physiological discussion. From the clinical standpoint, the decision of this question is not of immediate importance. In either case, the heart muscle together with the contained nerve cells constitutes an automatically contracting organ.

Effects of Vagus and Sympathetic Nerve Stimulation.—The heart receives extraneous nerve fibers from both vagi and from the cardiac sympathetic or accelerator nerves. Impulses conveyed by way of these nerves do not cause contractions of the heart directly, but they modify the fundamental properties of its muscle. In a general way, stimulation of the vagus depresses the fundamental properties, and particularly the tone (page 9), the rate of impulse formation and conduction, whereas stimulation of the sympathetic nerve acts in an opposite manner.

Clinical Methods for Studying the Cardiac Mechanism

The cardiac mechanism of man must ordinarily be studied by bloodless procedures. For this purpose two general methods are available. In the first, mechanical movements, produced by the heart or blood vessels, are recorded; in the second, records are made of the electric changes that accompany each wave of contraction as it sweeps over the heart muscle.

Mechanical Methods

Apex and Arterial Records.—Mechanical records may be taken from various points. Movements due to ventricular contractions may be recorded either from the arteries, or from the neighborhood of the heart itself. Apex and other records of movements of the chest wall usually show a large number of waves. The details of such curves vary considerably, not only in different individuals but in the same individual, according to the point examined, the posture of the patient and the recording methods used. Frequently it is difficult to determine the significance of the individual waves on such cardiograms. Nevertheless, apex tracings

possess one distinct advantage over arteriograms, for all ventricular beats are usually recorded, whereas, during irregular heart action, some ventricular systoles may fail to produce an appreciable arterial pulse. Arterial records, on the other hand, are preferable as standards of measurement, because the onset of the pulse wave is usually sharply defined, whereas the exact onset of the ventricular contractions is sometimes difficult to determine in apex tracings.

Venous Pulse.—The modern analysis of cardiac irregularities received its first great stimulus from James Mackenzie's extensive and systematic studies of the venous pulse in patients suffering from heart disease. In the venous pulse, waves produced by auricular and by ventricular activities can usually be recognized, and the time relationships between these permit an analysis of the mechanism of many cardiac irregularities. Similar

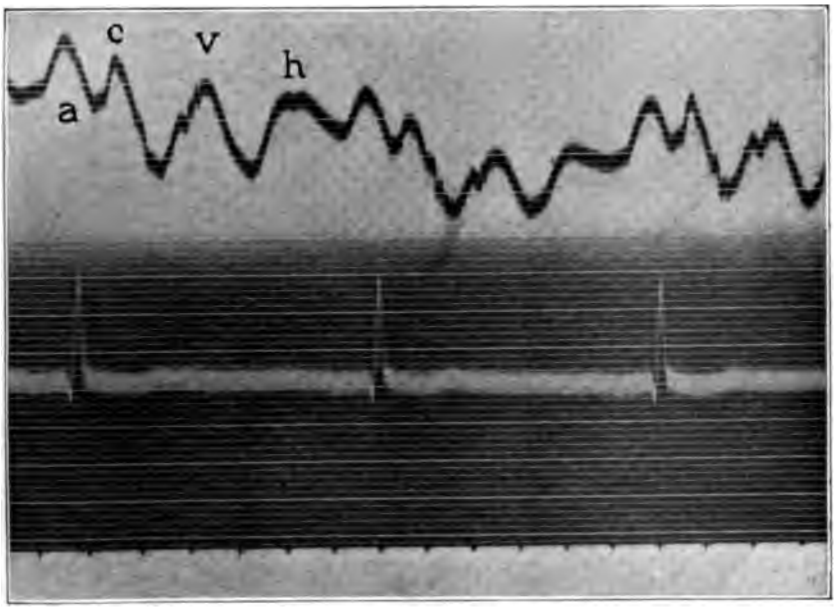


Fig. 19.—Normal Venous Pulse Showing a Well Marked h Wave. (This As Well As the Following Electrocardiograms Were Kindly Furnished by Dr. F. N. Wilson.)

records of auricular and ventricular systoles may be obtained under favorable conditions from the apex region, from within the esophagus, and from liver pulsations. For practical purposes, however, a record of the venous pulsations has proved the most serviceable of the mechanical methods for studying cardiac irregularities.

The Venous Waves.—The analysis of the jugular pulse is made with reference to a simultaneous record of the apex, the arterial pulse or the electrocardiogram. At about the time of the carotid pulse and about

0.1 second before the radial pulse, a wave is seen in the venous record, which is called the *c* wave. This is usually preceded by the *a* wave, and is followed by the *v* wave (Fig. 19). The *a* wave is due to the contraction of the right auricle, the *c* and *v* waves are expressions of ventricular activity. The fall of the *v* wave is produced by the opening of the tricuspid valves and the subsequent rush of blood into the right auricle. In slow heart rhythms there may also occur a well-defined pulsation after the *v* wave, the so-called *h* wave of Hirschfelder. In the analyses of most irregularities it is sufficient to remember that the *a* waves indicate auricular contractions, and that the *c*, *v* and *h* waves are referable to the activities of the ventricle. No definite significance can be attached to variations in the size of these waves.

Electrical Methods

Muscular Contraction and Electrical Changes. Electrocardiogram.—The second general method for studying the mechanism of the heart beat is the electrical method. Every muscular contraction is associated with electrical changes which begin as a primary negative electrical potential that travels over the muscle. In the voluntary muscle, the passage of this wave of negativity causes a diphasic electrical current that begins, and often ends, before the mechanical movements of the contraction have started. The electrical currents generated by the heart may be recorded by connecting a very sensitive galvanometer, such as the string galvanometer of Einthoven, to the extremities of the body. For this purpose three methods of leading off the current from the body are in general use: *Lead I,* from the two arms; *Lead II,* from the right arm and left leg, and *Lead III,* from the left arm and left leg.

Electrocardiograms from a normal individual usually show a series of waves called the *P, Q, R, S* and *T* waves (Fig. 20). Of these, *P* is evidence of auricular activity, while *Q, R, S* and *T* are produced by the activities of the ventricles. The electrocardiogram, like the venous pulse, enables one to recognize the time relationships between the auricular and ventricular contractions. In addition, however, the electrocardiogram indicates the direction in which contractions are spreading over the heart muscle. The *P* wave, for example, is normally upright in all leads, which indicates that the auricular wave of contraction travels from the right upper toward the left lower portion of the auricular muscle. A reversal of the *P* wave in all leads would indicate that the auricular contraction started from a point lying in the left lower part of the auricles; and any marked change in the site of origin, or in the path of conduction of the auricular contraction, will cause some change in the form of this wave in one or more leads.

Abnormal Ventricular Complexes.—Normal ventricular contractions

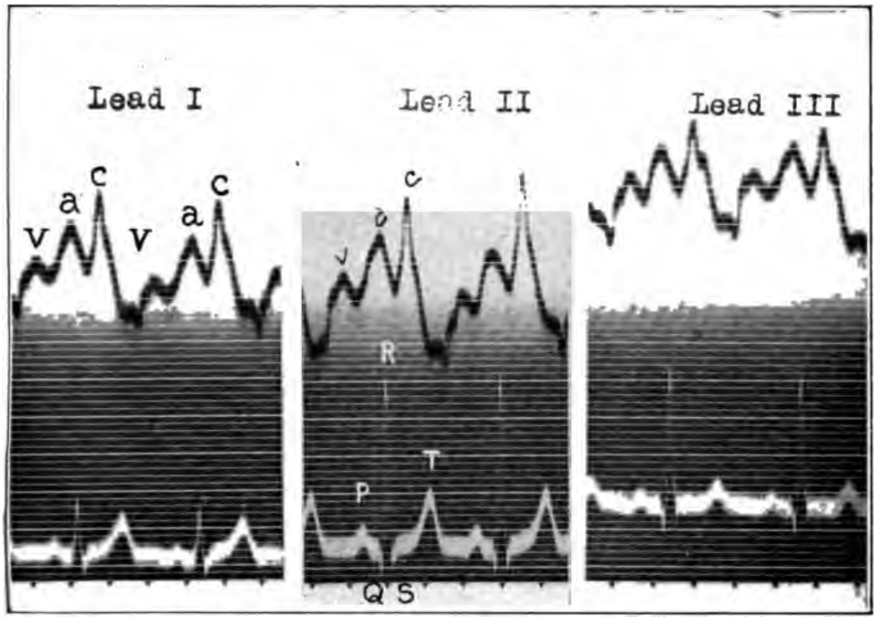


Fig. 20.—Normal Electrocardiograms. Note that R Is Highest in Lead II, Being Equal to the Sum of the Heights in Leads I and III.

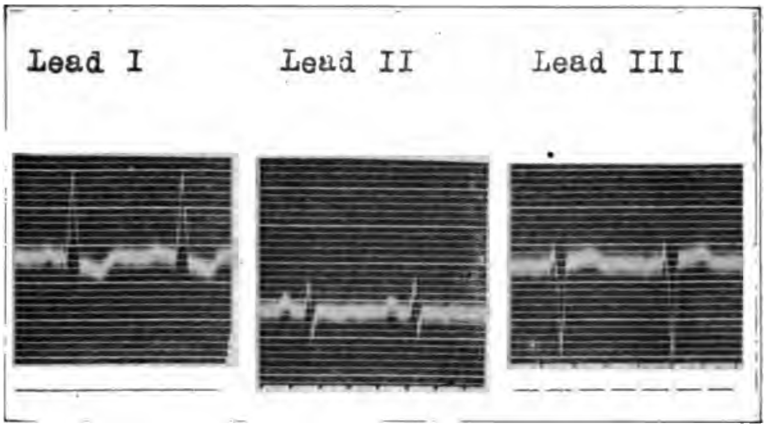


Fig. 21.—Electrocardiograms Characteristic of Left Ventricular Hypertrophy. From a Case of Aortic Insufficiency. Note the Small Size of R in Lead II and the Marked Downward Deflection in Lead III.

are produced by stimuli that enter the ventricles through the His bundle and spread through the ramifications of its branches in a normal manner. If the ventricular stimulus begins at some other point, or if it spreads through the heart muscle over abnormal paths, an abnormal electric

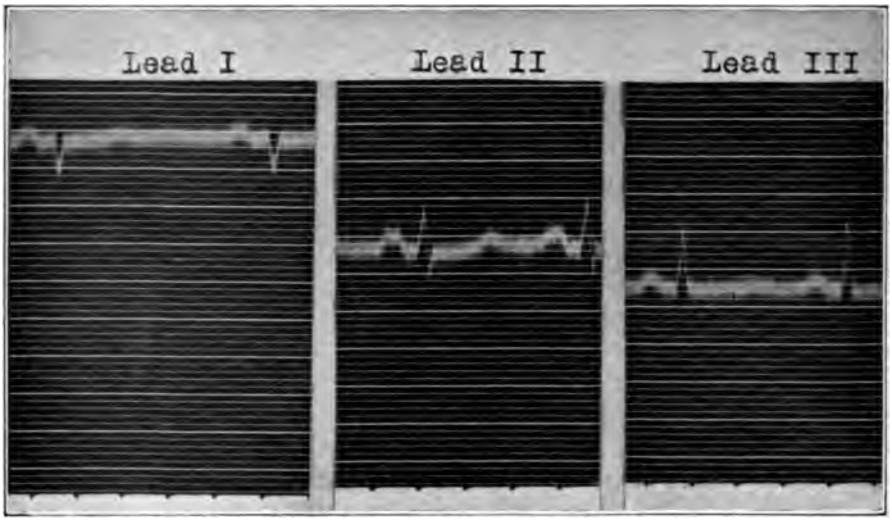


Fig. 22.—Electrocardiograms Characteristic of Right Ventricular Hypertrophy. From a Case of Mitral Stenosis. Note that R Is Highest in Lead III; Also the Downward Deflection in Lead I.

complex results. Modifications of the electric complex also result from hypertrophy of either ventricle (Figs. 21 and 22).

Sinus Variations in Rate and Rhythm

Moderately rapid and moderately slow heart rates without irregularity are usually due to changes in the rate of impulse formation in the sinus node. In such cases electrocardiograms and venous tracings show no departure from the normal, either in the site of the pacemaker or in the conduction of impulses over the heart.

The Normal Heart Rate

The average heart rate in healthy adults is about 70 beats per minute for men and about 80 beats for women. The rate is much faster in the new-born infant (130 per minute). It diminishes considerably during early infancy, and to a lesser extent during childhood and adolescence. In old age the rate may again increase, but whether this is to be regarded as a strictly physiological phenomenon, or whether it is dependent on the cardiovascular changes so common at this time of life, is not certain.

Variations of Pulse.—Individuals who are apparently normal may

show considerable variations from the average pulse rate. In some, the rate remains for years between 50 and 60 without evidence of disease, whereas, in others, rates of 90 or over may persist, even when such accelerating influences as emotion and exercise are eliminated. As a rule, however, rates much over 90 which persist when the patient is at rest in bed are pathological.

Causes of Variations.—Changes in the rate of impulse formation in the sinus node are due to various causes. These act either directly upon the sinus tissues, or they influence impulse formation through the vagus or accelerator nerves. In many cases changes in heart rate are due to a combined action of these nerves, for it is well known that when an organ receives both stimulating and inhibitory nerve fibers they frequently work in a coördinate manner.

Sinus Tachycardias

The rate of impulse formation in the sinus is normally subject to a more or less marked and continuous inhibition by way of the vagus nerves. If this tonic vagus inhibition be removed, either by cutting the vagi or by the administration of atropin or similar drugs, the sinus rhythm becomes more rapid. The subcutaneous injection of 1/60 grain of atropin in young individuals usually accelerates the pulse to about 130 a minute. When the same dose is administered to elderly persons, the acceleration is less marked and may be absent; apparently, because the tonic vagus inhibition of the sinus node is more pronounced in young individuals than in those who are older. A rapid heart rate due to the removal of vagus tone occurs clinically in the later stages of meningitis after the period of vagus stimulation has passed. It has also been described in patients with organic disease of the vagus nerves.

Exercise and Pulse Rate.—During exercise the pulse rate increases very promptly (Fig. 9). This primary rise of rate is due mainly to a diminution of vagus tone, which continues throughout the exercise. The increased rate during exercise may also be due in part to an increased activity of the accelerator nerve and to the increased temperature of the body. In certain pathological conditions exercise produces an excessive increase in the heart rate. This occurs particularly in nervous individuals, in those suffering from anemia and in those with cardiac insufficiency.

Heart Rate and Low Blood Pressure.—The increase of heart rate frequently associated with a low blood pressure seems to be due in part at least to a direct effect of the lowered pressure upon the medullary centers, for tachycardia may be produced experimentally by reducing the pressure in a completely isolated cerebral circulation.

Cardiac Insufficiency and Myocardial Disease.—In cardiac insufficiency and in myocardial disease the heart rate is frequently more rapid

than normal. In some instances, this increase may be due to disease in the region of the sinus node. More commonly, there is no reason to assume disease in this region, and the cause of the increased rate is not clear.

Fever.—An increase in the heart rate usually accompanies fever. In a general way, each Fahrenheit degree of fever causes an increase of seven to nine beats per minute. The rapid pulse of fever depends in part upon the rise of body temperature, which directly influences the rate of impulse formation in the sinus node, for we know that the rhythm of the isolated heart can be slowed or accelerated by cooling or warming the sinus region. The low blood pressure present in some infections may also play a part in causing an acceleration of the pulse. It is evident, however, that these are not the only factors which produce the pulse changes in infectious diseases, for in certain infections the heart is relatively rapid, whereas in others it is relatively slow. Thus, both tuberculosis and typhoid fever tend to reduce the blood pressure, yet the former is usually associated with a rapid pulse relative to the temperature, whereas the latter, in its earlier stages, is usually associated with a slow pulse. Such variations of rate in different infections must depend in part upon specific differences in the character of the infection.

Exophthalmic Goiter.—The tachycardia of exophthalmic goiter is apparently due to the toxic action of substances derived from the hyperactive thyroid gland, for a similar acceleration of the pulse may be produced in some individuals by the administration of thyroid substance. The mechanism that accelerates the heart in this disease is not definitely known, both stimulation of the accelerator nerve and a diminution in the tone of the vagus nerves having been held responsible. That the heart muscle may also be affected seems probable from the fact that, in the later stages of exophthalmic goiter, the patients not infrequently develop myocardial insufficiency, cardiac dilatation and cardiac irregularities.

Sinus Bradycardias

Slowing of the rate of impulse formation in the sinus node may be due to vagus stimulation. Acute asphyxia and acute increases of intracranial pressure slow the heart by stimulation of the vagus center in the medulla. The slow heart rate, commonly observed during the earlier stages of meningitis, is also due to stimulation of the vagus center either by the increased intracranial pressure, or by a direct irritation of the center by the inflammatory process. Vagus slowing of the heart may also be due to reflexes that arise from the nose, the eyeballs, or the abdominal organs. Various drugs and toxic substances slow the heart by their action upon the vagus nerve. Thus digitalis in large doses slows the sinus rhythm, although the therapeutic doses given to patients are rarely large enough to produce this effect.

Jaundice.—The slow pulse observed in certain cases of jaundice is also due to an increase of vagus tone. This has usually been attributed to the action of bile salts retained in the body, but, according to King and Stewart, it is due to the action of the bile pigments.

Acute Rises of Blood Pressure.—Acute rises of blood pressure also tend to slow the heart through vagus stimulation. They act directly upon the medullary centers, and also through reflexes from the heart and the aorta. In chronic hypertension, however, the heart rate is not slowed. Furthermore, during muscular exercise, it is accelerated despite the increase of blood pressure, mainly, as we have seen, because the vagus tone is lessened.

Convalescence from Febrile Diseases.—Bradycardia is frequently observed during convalescence from febrile diseases, and particularly after typhoid fever, pneumonia, scarlet fever, etc. This bradycardia is frequently associated with a respiratory vagus irregularity, which favors the view that it is due to an increase in the vagus tone. According to Dehio, however, the injection of atropin in such patients frequently produces no acceleration of the pulse and this author, therefore, concludes that the postfebrile type of bradycardia is due to changes in the heart muscle, rather than to an increase in the vagus tone.

Sinus Arrhythmias

Respiration Arrhythmia.—When a young individual breathes slowly and deeply, the pulse is more rapid during inspiration than during expiration, and this difference may be so marked that it constitutes a definite arrhythmia (Fig. 23). During inspiration the rate becomes in-

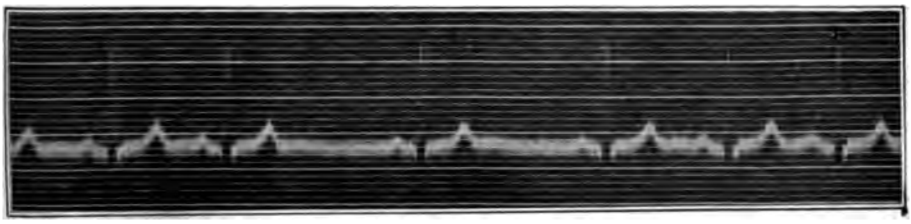


Fig. 23.—Respiratory Irregularity in a Young Adult. The Waves Are Normal.

creasingly more rapid, but shortly after the onset of expiration it slows down rather abruptly. Gradually the beats become more and more accelerated and thus the cycle is completed. Graphic records show that, during such an irregularity, the pacemaker remains in or near the sinus node and the contraction wave spreads over the heart in the normal manner. Such irregularities are, therefore, spoken of as sinus arrhythmias.

Pathogenesis.—Respiratory variations in the heart rate occur not

only in man but in certain animals. They may be made to disappear if the vagi are cut or if sufficiently large doses of atropin are given. Hence they are caused by variations in the vagus control of the heart. They appear to be due in part to reflexes arising from the chest during respiration; but since they continue even though the thorax be widely opened, the reflexes from the thorax cannot be their sole cause. Apparently there is, in addition, a radiation of stimuli from the respiratory to the vagus center in the medulla, which influences the vagus control of the heart rate.

Migration of Pacemaker.—We have said that in this type of irregularity the pacemaker remains in or near the sinus node, and that the contraction wave spreads over the heart in the usual manner. Electrocardiographic records from man as well as from animals show, however, that in certain individuals the vagus slowing during deep breathing, as well as

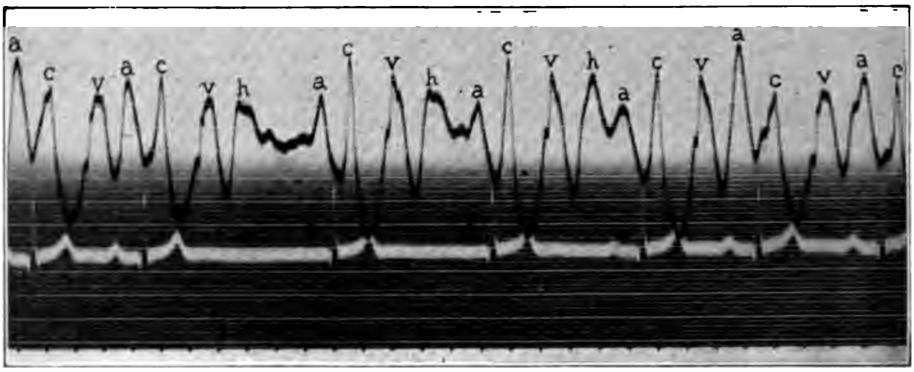


Fig. 24. Respiratory Irregularity in a Young Adult. Lead III. During Expiration the Heart Rate Slows and the P Wave Almost Disappears (See Arrows). The Venous Pulse Indicates, However, that the Auricle Is Contracting Normally.

the vagus slowing from direct or reflex stimulation of the vagus nerve, may cause a flattening or even an inversion of P in the second, and particularly in the third leads (Fig. 24). Eyster and Meek have shown that in the dog vagus stimulation may cause a migration of the pacemaker from the upper to the lower portion of the sinus node. Since such a migration would tend to reduce the size of P, particularly in the third lead, it seems not improbable that the changes in the form of P observed in man may be due to such a migration of the pacemaker in a downward direction.

Other Forms of Sinus Arrhythmia.—The most common type of sinus irregularity is that associated with respiration. Other forms also occur. After swallowing, for example, there may be a vagus slowing of the heart. In certain individuals the heart is continuously undergoing more or less marked fluctuations in rate which seem to depend upon an unusually labile control of the heart by the vagus nerve.

Sinus arrhythmias are observed particularly in young individuals and they have, therefore, been called by Mackenzie the *youthful irregularities.* As a person grows older, the heart becomes less and less subject to vagus control, and drugs that lessen the vagus control, such as atropin and amyl nitrite, produce less and less acceleration of the heart. At the same time vagus irregularities tend to disappear. Sinus irregularities occur not infrequently during the *convalescence from acute infections,* and they are often associated with the postfebrile type of bradycardia. Since they may be made to disappear by the injection of atropin, they are of nervous origin and have no unfavorable significance so far as the heart muscle is concerned. Sinus irregularities are particularly common in *nervous* individuals, both in association with deep respirations and as apparently spontaneous fluctuations in the heart rate. They are closely related to other manifestations of nervous instability and irritability, such as an exaggeration of the tendon reflexes, excessive vascular reactions after irritation of the skin, hippus, etc.

Disturbances of Conduction

It will be recalled that the stimuli which cause the cardiac contractions are first conducted from the sinus node to the auricular muscle and to the auricular terminations of the auriculoventricular bundle of His. The latter is the sole functional connection between the auricles and ventricles. After entering the interventricular septum this bundle divides into two branches that supply the right and the left ventricles respectively. Disturbances of conduction may give rise: (1) to a *retardation* in the transmission of the stimulus; (2) to an occasional interruption to its transmission or *partial block;* and (3) to a complete interruption in its transmission or *complete block.* In general, it may be said that stimulation of the vagus nerve diminishes conductivity, whereas stimulation of the accelerator nerve improves it.

Sino-auricular Block

Inasmuch as it is impossible to record the isolated activity of the sinus region in mammals either by mechanical or electrical methods, the evidence for a disturbance of conduction between the sinus node and the auricular muscle is of an inferential character. Erlanger has shown that by torsion of the sinus region it is possible to cause an occasional omission of auricular beats, presumably because the stimulus from the sinus was unable at times to cross the twisted tissues. Eyster and Meek found that when morphin was administered to the dog certain irregularities occurred, which were best explained on the hypothesis that the vagus stimulation caused by morphin had interrupted the progress of impulses from the sinus

to the auricle. Sinus blocks in man have also been occasionally observed and particularly in patients who have been receiving digitalis. In Figure 25, for example, it will be seen that there is a long pause between the *P*

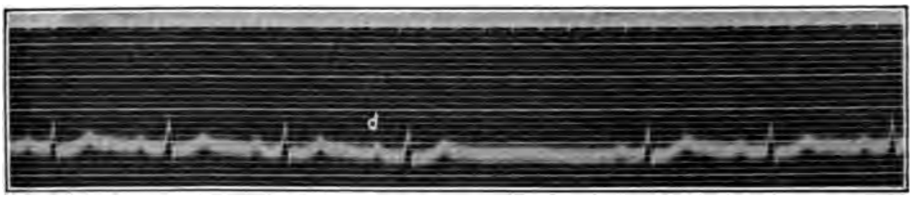


Fig. 25.—Sino-auricular Block. During the Intermission There Is No Contraction of the Auricle and the P Waves Are Separated by Twice the Normal Distance.

waves, and that the duration of this pause is approximately twice that which separates the normal auricular beats. Presumably in such cases there has been an occasional block of the impulse coming from the sinus node.

Auriculoventricular Block

Lengthened As-Vs Interval

As evidence of an imperfect conduction of stimuli from the auricles to the ventricles, we may find an unusually long interval between the contractions of the auricles and the contractions of the ventricles. This is evident on the venous pulse by a prolongation of the interval between the *a* and *c*

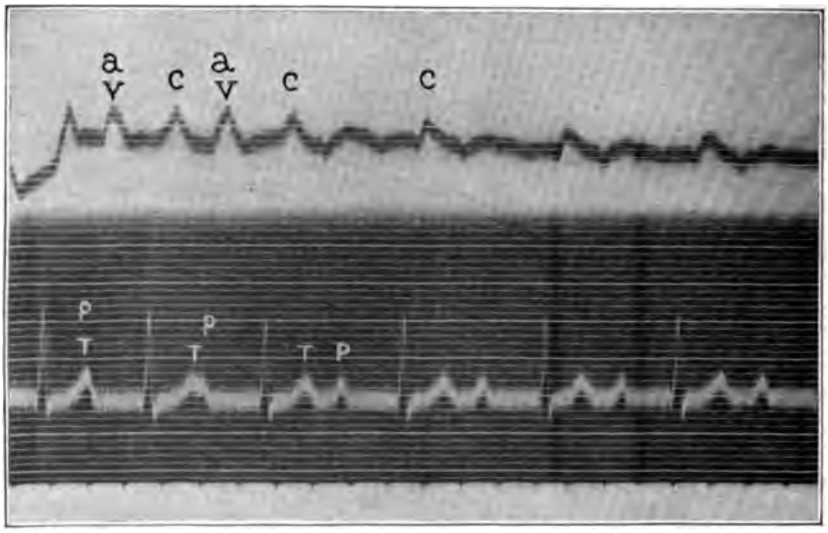


Fig 26.—Lengthened Vs-As Interval (About 0.37 Second). When the Heart Action Is Rapid *a* Falls on *v* and P on T. When the Action Is Slow P and T Are Separated and the *a* and *v* Waves Flatten Out.

waves, and on the electrocardiogram by an unusual interval between *P* and *R*. Normally these intervals do not exceed 0.2 second, but in pathologic cases they may be increased to 0.35 second or more (Fig. 26).

Partial Block

When the conductivity is more definitely impaired, stimuli occasionally fail to pass from the auricles to the ventricles and the corresponding ventricular beats drop out. Such a partial block is often preceded by a gradual lengthening of the *a-c* or *P-R* intervals, indicating that impulses are passing over the His bundle more and more slowly. Finally, the impulse fails to pass over and a ventricular beat drops out. Following this block, the conduction time between auricles and ventricles is usually shortened (Fig. 27), presumably because the conducting system has rested during the block. In some cases, however, partial heart block is not associated with any demonstrable change in the length of the *As-Vs* interval.

In more advanced stage of partial heart block, ventricular systoles are

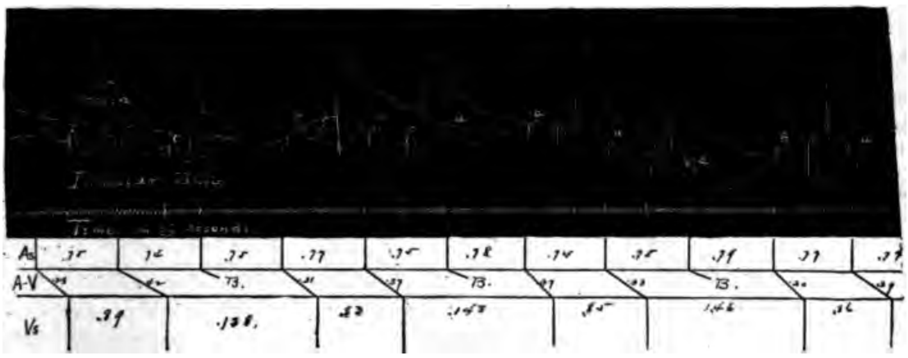


Fig. 27.—Partial Heart Block. Each Third Ventricular Contraction Is Omitted. Note that the a-c Time (A-V) Is Shortened after Each Block and that It Lengthens Before the Block Occurs.

dropped out frequently. A definite ratio tends to become established between the auricular and ventricular rates. For example, there may be three auricular to two ventricular systoles, a three to two ratio, or there may be ratios of two to one, three to one, etc. (Fig. 27).

Complete Heart Block

In cases of partial heart block the ventricles respond to impulses received from some, but not all, of the preceding auricular contractions. When the block is still more marked, all functional connection between the auricles and the ventricles is interrupted. This condition is known as

complete heart block or auriculoventricular dissociation. Left to themselves, the ventricles develop an automatic idioventricular rhythm, which usually has a rate of from 30 to 40 per minute and is perfectly regular (Fig. 28). The electric ventricular complexes during complete dissociation are most frequently of a normal character. This indicates that the idioventricular rhythm is initiated from some point in the His bundle above its division, and that the impulses travel to the ventricular muscle over the usual paths.

Occasional idioventricular beats have been observed in patients with an unusually slow heart rate due to various causes. Owing to the long diastolic pauses, opportunity is given for the inherent automatic rhythm of the ventricles to manifest itself. It is evident that this will occur more readily when for any reason the inherent rhythm of the ventricles is accel-

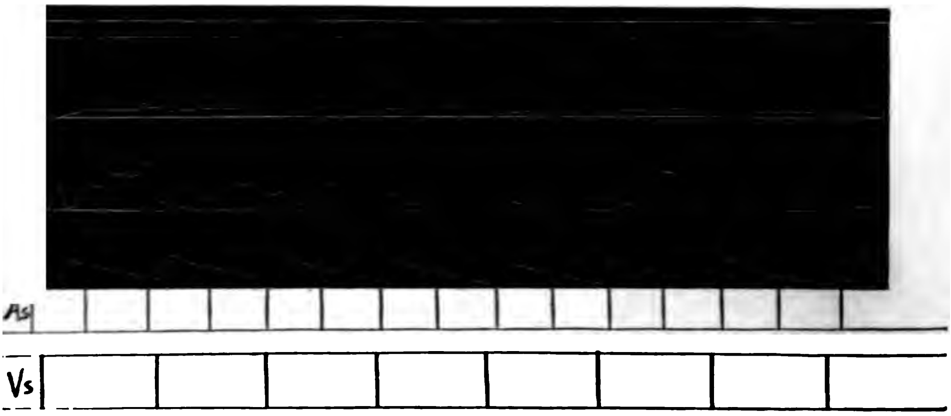


Fig. 28.—Complete Heart Block. Note that the Auricles and Ventricles Are Beating Independently. The Ventricular Rhythm Is Regular and about 40 per Minute.

erated. Toxic doses of digitalis when given to animals seem to increase the idioventricular rate, for in the late stages of digitalis poisoning, there may be a complete dissociation between auricles and ventricles with such a rapid ventricular rhythm that it may even exceed the rhythm of the auricles. This rapid ventricular rhythm appears to be due to an action of digitalis upon the heart muscle. The administration of therapeutic doses of digitalis to patients with complete heart block causes no slowing of the ventricular rate. Only occasionally does it cause an acceleration, such as has been produced by the administration of toxic doses to animals.

Nervous Control of Idioventricular Rate.—To what extent the idioventricular rate is under nervous control has been much discussed and is still unsettled. In patients with complete heart block the ventricular rate may usually be increased by vigorous muscular exercise or by fever, presumably from an action of the accelerator nerves or a direct effect upon

the heart muscle. On the other hand, neither the injection of atropin nor stimulation of the vagus nerve ordinarily influences the ventricular rate in complete heart block, though in some cases apparently a slowing has been produced by vagus stimulation. Possibly vagus fibers running in or near the His bundle are frequently damaged by the lesion that produces the block, and this accounts for the varying observations. In any case, it is certain that the vagus exercises less influence upon the idioventricular rhythm than it does upon that which originates in the sinus.

Blocks in Branches of the His Bundle

Eppinger and Rothberger showed that if one branch of the His bundle be cut, characteristic changes are produced in the electrocardiogram owing to the abnormal manner in which impulses spread to the ventricles. When

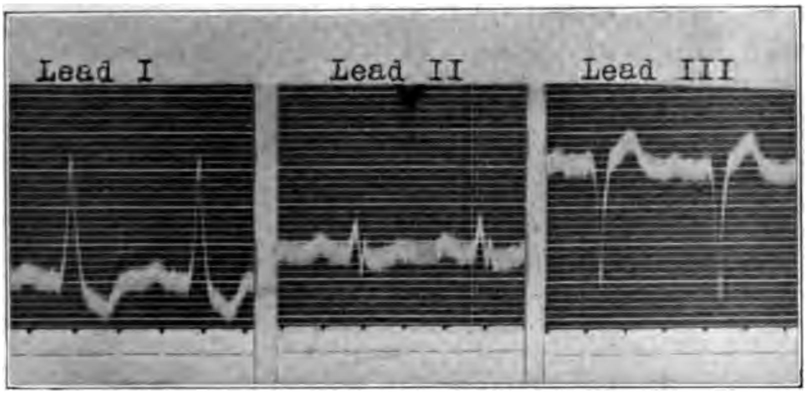


Fig. 29.—Block in the Right Branch of the His Bundle. Note the Diphasic Character in Leads I and III. Also the Two Apices of R in Lead II.

the right branch is cut the ventricular complexes resemble those which result from ectopic beats that originate in the left and apical region of the heart. When the left branch is cut, the ventricular complexes resemble those which result from abnormal beats that originate in the right and basic portion of the ventricles. Clinical cases showing similar changes have been observed (Figs. 29 and 30). According to Carter, slight disturbances in the conductivity of one branch of the His bundle are by no means infrequent.

Causes of Auriculoventricular Block

(*a*) *Nervous and Toxic*

Stimulation of the vagus nerves frequently produces a partial heart block. As a rule, stimulation of the left vagus exerts a greater influence

upon the conductivity of the His bundle than does stimulation of the right vagus, whereas stimulation of the right vagus usually exerts a greater influence upon the rate of impulse formation in the sinus node.

In man, partial block has been produced repeatedly in susceptible individuals by pressure upon the vagus nerves in the neck, and particularly by pressure upon the left vagus. It has also been produced reflexly by pressure on the eyeballs. In susceptible individuals partial block has been observed during the increased vagus activity that follows swallowing, and during the slow heart action accompanying expiration.

The therapeutic administration of large doses of digitalis and of allied drugs also produces partial heart block in certain patients. That this block is due largely to an increased activity of the vagus nerve has been demon-

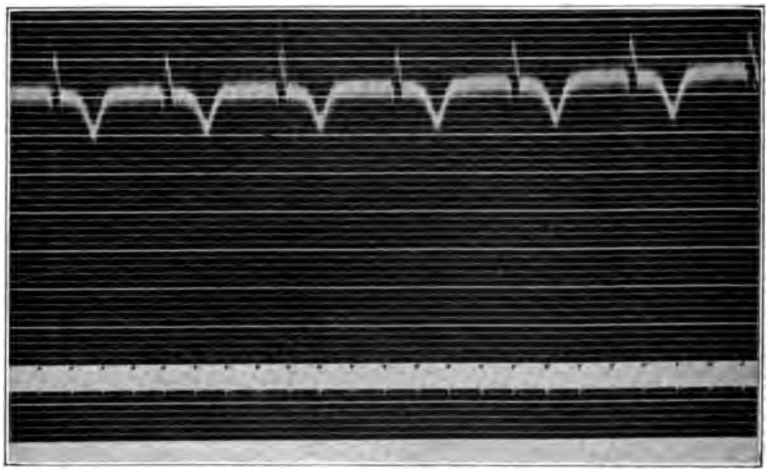


Fig. 30.—Probably a Block in the Left Branch of the His Bundle. Lead III. Note the Diphasic Character of the Ventricular Complex which Is Opposite in Type to that Seen in Fig. 29, Lead III. Complicated by an A-V Rhythm. P Is Not Seen.

strated by the fact that it frequently disappears after atropin injections. But digitalis also affects the heart muscle. Cohn has shown that therapeutic doses given to patients change the form of the *T* wave. The heart block that develops during late stages of experimental digitalis poisoning cannot be removed by atropin, and in some patients also atropin may not remove a digitalis block. It seems certain, therefore, that this block is due in part to vagus stimulation, and in part to the direct action of digitalis upon the conducting fibers in the heart.

Partial heart block has been produced in dogs by morphin injection and is here due to vagus stimulation.

In acute asphyxia, partial heart block may also occur. Acute asphyxia stimulates the vagus center in the medulla, and a slowing of the sinus rhythm during asphyxia is due in part to this stimulation. Mathison has

shown, however, that the partial heart block of acute asphyxia is due, not to vagus stimulation alone, but to a direct toxic effect upon the heart muscle.

(*b*) *Organic Causes*

Erlanger showed that by gradually compressing the His bundle varying degrees of block can be produced. As the pressure is increased there occurs first a lengthening of the *A-V* interval, then occasional or frequent interruptions of the stimuli passing to the ventricles (partial block), and finally a complete dissociation between auricles and ventricles. In a similar manner local organic lesions in the region of the His bundle may produce all degrees of block. These lesions may consist of fibrous tissue, localized myocarditis, an acute abscess, a gumma or a tumor. Complete heart block is, as a rule, due to an organic injury to the His bundle, although in some cases no organic lesion has been found. Partial block, on the other hand, may be due to organic lesions, or to toxic or nervous influences, or it may be due to any combinations of these.

Ectopic Beats, Extrasystoles

Cardiac contractions that originate at some point other than the sinus node are spoken of as ectopic beats. These may occur singly or in rapid succession. They may originate in the auricles, the auriculoventricular tissues or the ventricles. Premature beats or extrasystoles are beats which interrupt an otherwise regular heart action by occurring prematurely. They usually arise at some point outside of the sinus node and are, therefore, ectopic beats as well.

Homogenetic Beats and Rhythms

According to Lewis, two types of ectopic beats should be distinguished. When for any reason impulse formation in the sinus node is inhibited, or the impulses there formed are interrupted in their passage over the cardiac muscle, the function of pacemaker may be taken up by some other part of the heart. The new pacemaker under these circumstances is usually some part of the auriculoventricular node or of the His bundle. Ectopic beats or rhythms of this character are spoken of by Lewis as homogenetic in type, for they are due to a dormant normal rhythm that is ordinarily masked by the predominant sinus rhythm.

We have seen, for example, that, in complete heart block, an opportunity arises for the development of an ectopic ventricular rhythm, which takes its origin from the main stem of the His bundle. Similarly, a depression in the rate of impulse formation at the sinus node may permit the formation of spontaneous impulses of a regular type from the upper portion of the auriculoventricular conducting system. Rhythms of this

type have been produced experimentally by cooling the sinus tissues, and they occur occasionally during vagus stimulation, particularly when this is associated with a stimulation of the left accelerator nerve. Wilson has

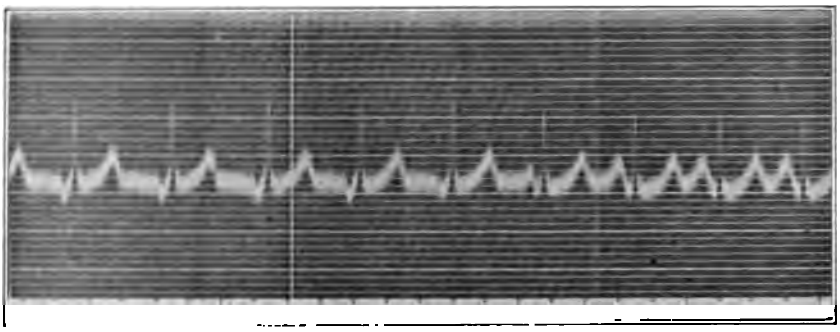


Fig. 31 Rhythm Proceeding from the Upper Part of the A-V Node with Transition to Normal Rhythm Atropin Effect. Note that during the Abnormal Rhythm P Is Inverted and the P-R Interval Is Shortened.

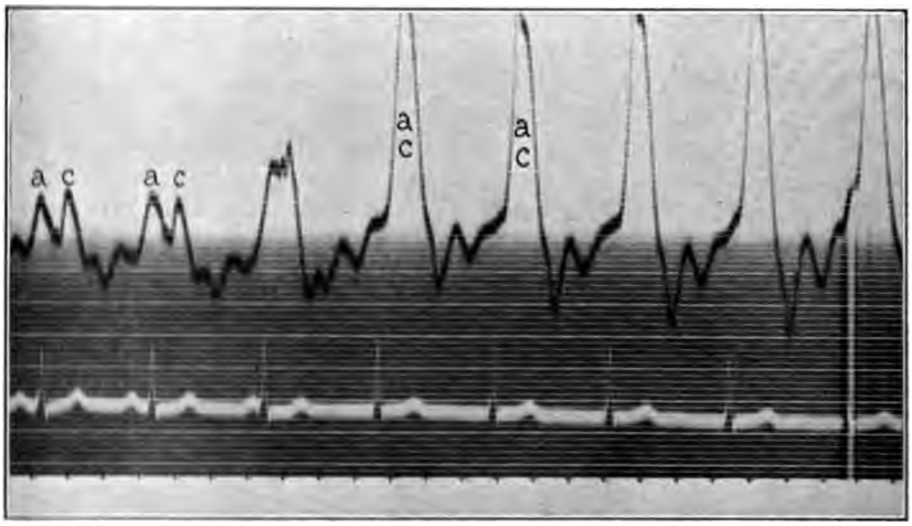


Fig. 32 Rhythm Proceeding from the A-V Node with Transition from the Normal Rhythm. The Pacemaker in this Case Is Somewhat Lower than in Fig. 31. The Auricles and Ventricles Contract Simultaneously, Causing a High Wave, Owing to the Fact that the Auricles Are Unable to Empty into the Contracted Ventricles and Expel their Contents into the Veins. P Is Lost in the Ventricular Complex.

recently shown that in man the pacemaker occasionally shifts to the *a-v* node during the expiratory phase of forced respirations, and that this occurs in a considerable proportion of normal young individuals about ten minutes after the injection of 1/60 grain of atropin (Figs. 31 and 32).

Heterogenetic Beats

The more common types of ectopic beats, called by Lewis heterogenetic, do not represent a dormant normal rhythm but are entirely abnormal. These may also arise from the specialized tissues joining the auricles and ventricle. More commonly, however, they arise in other parts of the heart muscle. Heterogenetic beats possess certain characteristics that serve to distinguish them from homogenetic beats: (1) they usually occur singly; (2) they occur relatively early after the preceding systoles and are, therefore, premature beats or extrasystoles; and (3) such beats are usually not affected by measures which influence the rate of impulse formation in the sinus or *a-v* tissues. The essential difference between homogenetic and heterogenetic beats is illustrated by the action of potassium salts, which depress the normal rhythms but which may cause heterogenetic beats.

Auricular Extrasystoles

Premature ectopic beats may arise from any portion of the auricular muscle. The auricular contraction thus initiated usually sends a stimulus

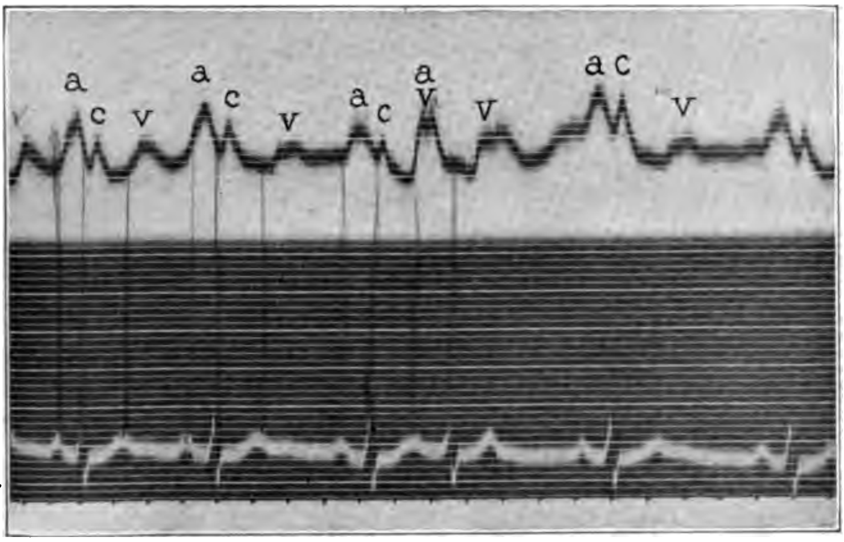


Fig. 33.—Auricular Extrasystole. The Premature Contraction of the Auricle Causes a Summation of *a* and *v* As Well As of P and T. The Pause after the Extra Beat Is Only Slightly Longer than the Normal Interval Between Beats.

to the ventricles, so that these chambers also participate in the premature contraction (Fig. 33). When auricular extrasystoles follow normal beats by very short intervals, the transmission of the stimuli to the ven-

tricles is usually delayed, and occasionally the ventricles fail to follow the premature auricular contractions (blocked auricular extrasystoles).

Auricular extrasystoles usually take their origin from some point well outside of the sinus node, for the *P* wave in the electrocardiogram is usually abnormal in one or more leads. Auricular extrasystoles discharge the sinus region of the material which has been accumulating there for the production of the next normal systole. After its discharge this material begins to accumulate again, and the next normal auricular contraction usually follows the extrasystole by a slightly greater interval than that which intervenes between the normal beats.

Auriculoventricular Extrasystoles

Premature beats, arising in the junctional tissues that connect the auricles and the ventricles, are infrequent. Such premature contractions are characterized: (1) by premature contractions of both auricles and ventricles; (2) by a shortened time interval between the contractions of auricles and ventricles; and (3) by an inversion of the *P* wave in the second and third leads of the electrocardiogram because the stimulus originates near the lower portion of the auricular muscle.

Ventricular Extrasystoles

Extrasystoles arise most commonly from some part of the ventricular musculature. When the ventricles contract prematurely the auricular rhythm is usually not disturbed. The impulse from the succeeding normal auricular contraction usually reaches the ventricles during the refractory period that immediately follows their extrasystole, and consequently it causes no ventricular contraction. Ventricular extrasystoles are, therefore, usually followed by a pause which lasts until the next stimulus arrives from the auricles. Since the auricular rhythm has not been disturbed, the time intervening between the normal ventricular systole immediately preceding and that immediately following the extrasystole is twice the interval between normal beats. There is, therefore, said to be a *full compensatory pause* after the extrasystole (Fig. 34). In this respect ventricular extrasystoles differ from those which arise in the auricles, for in the latter the compensatory pause is either absent or is shortened.

In the electrocardiogram ventricular extrasystoles are usually readily recognized by their aberrant form. This form varies greatly, but two main types have been distinguished. The first of these is similar to that which can be produced experimentally by stimulation of the basal portion of the right ventricle. The second type is similar to that produced experimentally by stimulation of the apex of the left ventricle. These are illustrated in Figure 34. These marked deviations from the normal type of

ventricular complex are due to the fact that the stimulus, instead of entering the ventricles through the His bundle and its branches, arises from

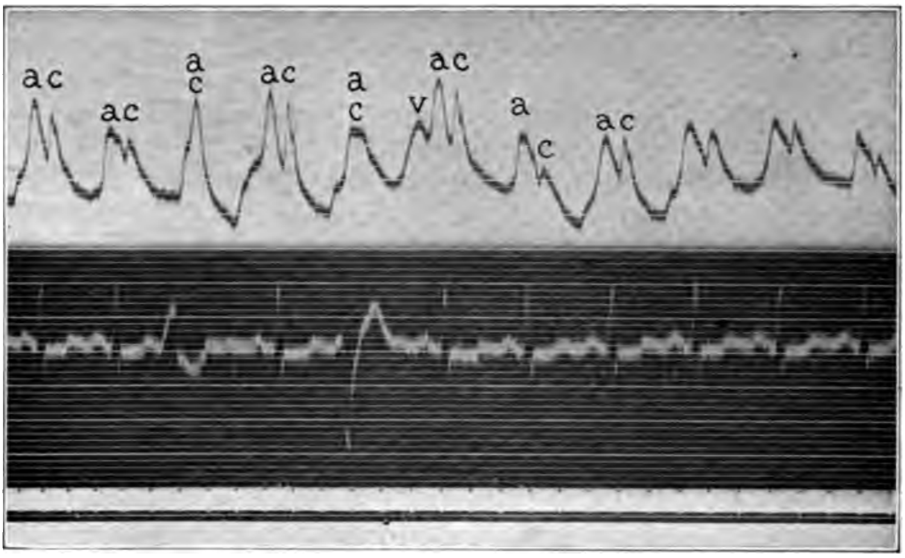


Fig. 34.—Ventricular Extrasystoles. Two Types Are Seen. Note their Diphasic Character. The Premature Ventricular Contraction Causes the *c* Wave to Fall upon the a Wave in the Venous Pulse. There Is a Full Compensatory Pause Because the Auricular Rhythm Is Not Disturbed.

some part of the ventricular muscle and spreads over these chambers in an abnormal manner.

Interpolated Ventricular Extrasystoles

In some cases ventricular extrasystoles occur so long before the next normal stimulus arrives from the auricle that the latter reaches the ventricle after the extrasystolic refractory period has passed. In such cases, the ventricular extrasystole is interpolated between two ventricular beats that are separated by a normal interval (Fig. 35).

Retrograde Extrasystoles

Ordinarily ventricular extrasystoles do not disturb the auricular rhythm. Occasionally, however, and particularly when a series of ventricular extrasystoles occur in rapid succession, the impulses may be transmitted in a retrograde direction over the His bundle, so that the auricles contract in response to stimuli coming from the ventricles. These are called retrograde extrasystoles (Fig. 36).

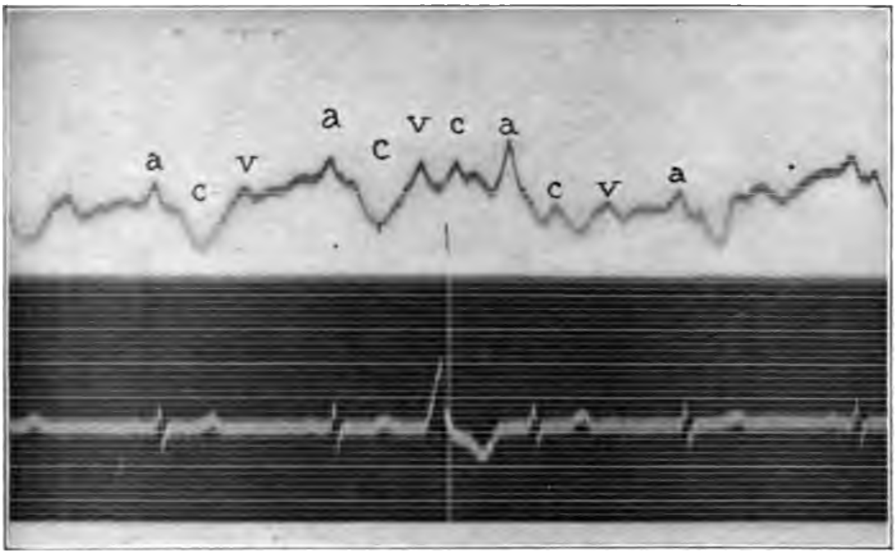


Fig [illegible] Interpolated Ventricular Extrasystole. Note that the Heart Rhythm Is Disturbed Only by the Addition of the Ventricular Beat and that the Next Auricular Contraction Causes the Usual Ventricular Systole.

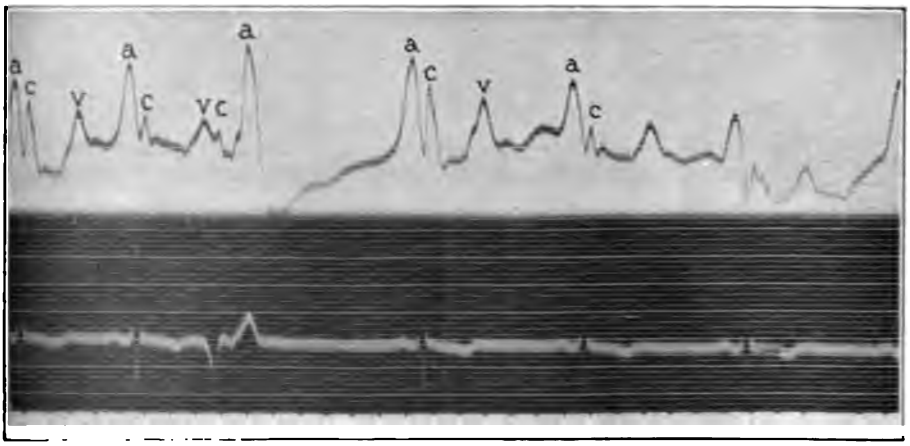


Fig [illegible] [illegible] Extrasystole. The Premature Ventricular Contraction Is Followed by [illegible] Contraction, Owing to a Transmission of the Stimulus [illegible] the His Bundle.

Recurrence of Extrasystoles

Extrasystoles are the most capricious of all cardiac irregularities. In a single patient they may be very numerous on one occasion, while, at another time, they may occur only occasionally or be absent altogether. Such changes may take place rapidly and frequently and often with no apparent cause. Extrasystoles, when present, may be scattered irregularly among the normal beats, or they may recur in a more or less regular manner, as, for example, after every fifth or seventh normal contraction. When extrasystoles alternate with normal contractions, there is a grouping

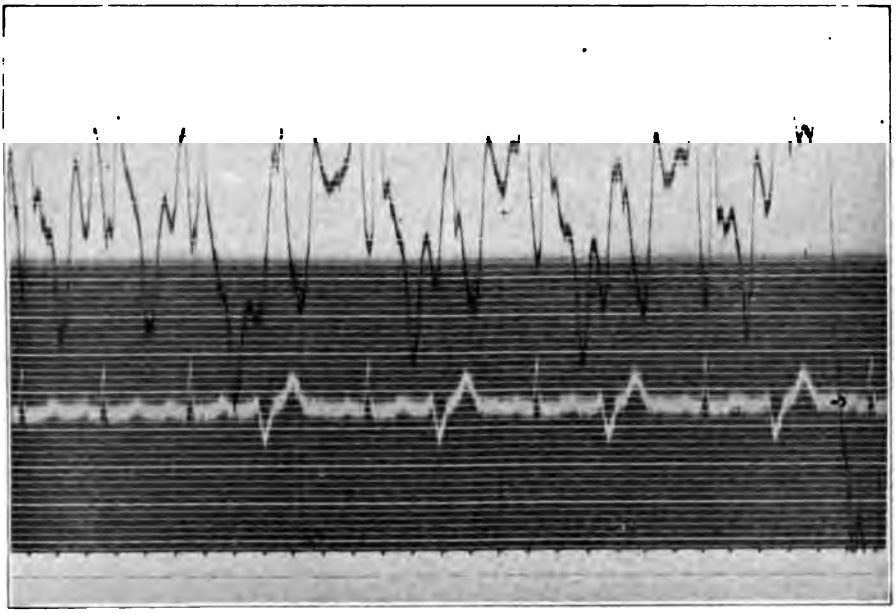


Fig. 37.—Transition from a Normal Rhythm to a Pulsus Bigeminus which Is Caused by the Regular Occurrence of a Ventricular Extrasystole after each Normal Beat.

of beats into twos, the so-called pulsus bigeminus (Fig. 37). When they follow every second normal contraction there is a grouping of beats into threes, the so-called pulsus trigeminus.

Pathogenesis of Extrasystoles

Experimentally, extrasystoles have been produced by electrical, mechanical and chemical stimulation of the heart muscle. When the thoracic aorta is clamped, the ventricular extrasystoles, that usually occur, appear to result from the rapid mechanical distention of the left ventricle. Various toxic substances also produce extrasystoles when injected into animals. Among these are potassium and barium salts, digitalis, chloroform, etc. An interference with the blood supply to the

heart muscle, produced by ligation or embolism of the coronary artery, may also cause extrasystoles.

Nervous Stimuli.—It is doubtful if extrasystoles can be produced in normal hearts by stimulation of the cardiac nerves. Such stimulation, as we have seen, may cause the pacemaker of the heart to shift from the sinus region to the region of the auriculoventricular node; but this appears to be due to changes in the automatic physiological rhythms of these regions. The resulting ectopic beats have neither the capricious, nor the markedly premature character of typical extrasystoles. Lewis believes, therefore, that this change in the pacemaker is of a homogenetic rather than a heterogenetic character. In hearts already showing a tendency to extrasystoles, nervous stimuli may, however, play a part in exciting these irregularities.

Anatomical Changes in Heart Muscle.—In man, extrasystoles are relatively common in patients who may be suspected of having anatomical changes in the heart muscle. In coronary sclerosis, myocardial insufficiency, and in the acute myocarditides associated with infectious diseases, extrasystoles are relatively common. Ventricular extrasystoles are frequently encountered in patients with chronic hypertension. These may be due in part to the mechanical stimulus of the high pressure, and in part to changes in the nutrition of the heart muscle. Similarly, the auricular extrasystoles observed in mitral disease may be due in part to the high intra-auricular pressure, and in part to changes in the auricular muscle.

Toxic Causes.—Extrasystoles in man may also be due to toxic causes. In some cases, they seem to be associated with the abuse of tobacco or of coffee, or with the administration of digitalis. Occasionally, cases have been reported in which extrasystoles were associated with psychic or nervous disturbances. Such cases are rather uncommon, however, and it is difficult or impossible to exclude a coincident toxic or organic damage to the heart muscle. It seems not improbable, however, that in exceptional cases extrasystoles in man may be excited by nervous causes.

Two Hypotheses.—In exactly what manner toxic or nutritional disturbances give rise to extrasystoles is not known. Experimentally, they may result from the application of electrical or mechanical stimuli to the heart muscle, and it is usually assumed that in man also extrasystoles result from some *abnormal stimulation, or from some local increase in the irritability of the heart muscle.* It is difficult to understand, however, why such causes should produce occasional premature beats rather than a succession of such beats. Possibly some part of the heart muscle is not fully discharged with each systole, and the accumulation of unstable material at this point causes an occasional discharge. The disturbance in such a case would be due to a *change in the conductivity of a limited portion of the heart muscle* rather than to a change in its irritability.

In any event it is evident that extrasystoles may arise from a very

minute portion of the heart muscle. The irregularity, therefore, does not in itself indicate any widespread disease of the heart.

Prognosis.—The prognosis of extrasystoles is varied. When due to nervous influences, to toxic substances, or to acute myocardial changes, complete and permanent disappearances of the irregularity is possible. When due to chronic nutritional changes that result from coronary disease or chronic myocarditis, complete and permanent disappearance is less probable. In general, the first group of causes are more common in young individuals, while the second group are more common in elderly individuals. For this reason, young individuals are more likely ~~apt~~ to lose their extrasystoles than older persons. The effect of extrasystoles upon cardiac efficiency depends mainly upon the frequency with which they occur. As a rule, premature ventricular beats expel less blood into the arteries than do normal beats and, in some cases, they produce no arterial pulse whatever. When such a diminution or disappearance of the pulse occurs occasionally, it does not seriously impair the circulation. Where it recurs frequently, however, the extrasystoles may in themselves contribute to a cardiac insufficiency.

Rapid Ectopic Rhythms

In discussing the pacemaker of the heart we have seen that this may pass from the normal sinus region to an abnormal site: (1) because a slowing of the sinus rhythm, or an interference with its conduction to other parts of the heart, allows some other region to assert its normal inherent rhythm (homogenetic ectopic rhythms); or (2) because some other part of the heart develops a pathological rhythm, which is so rapid that it usurps the function of pacemaker from the normal sinus region (heterogenetic ectoptic rhythms). Heterogenetic rhythms are in general characterized by their extreme rapidity. They are closely related to extrasystoles. The latter, as we have seen, usually occur singly, but they may occur in runs of two or more abnormal beats. From such short runs there are all degrees of transition to those cases in which a prolonged series of abnormal beats follow one another for hours or days. The intimate relation of the latter conditions, which are spoken of clinically as paroxysmal tachycardia and auricular flutter, to isolated extrasystoles, is apparent from the fact that isolated extrasystoles not infrequently occur after paroxysms of tachycardia have terminated.

Paroxysmal Tachycardia

Paroxysmal tachycardia is characterized clinically by a very rapid heart rate, which begins and terminates suddenly. It is due to a rapid succession of ectopic beats, which usually arise from some point in the auricles. The *P* waves are usually abnormal in one or more leads, indi-

cating an origin from some other point than the sinus region. As a rule, each auricular beat is followed by a ventricular contraction, and the rate during the paroxysm usually lies between 140 and 220 a minute. Patients who are subject to paroxysmal tachycardia not infrequently show auricular extrasystoles between the paroxysms, and these are particularly frequent just before or just after a paroxysm. Such auricular extrasystoles may arise from the same region of the auricular muscle as that which gave rise to the paroxysm.

Paroxysmal tachycardias may also originate in the ventricles, but these are relatively uncommon and long paroxysms of this type have not been described.

Retarded Conduction of Impulses.—Owing to the rapid succession of auricular beats during the paroxysms, there is frequently a retardation in the conduction of impulses from the auricles to the ventricles. On

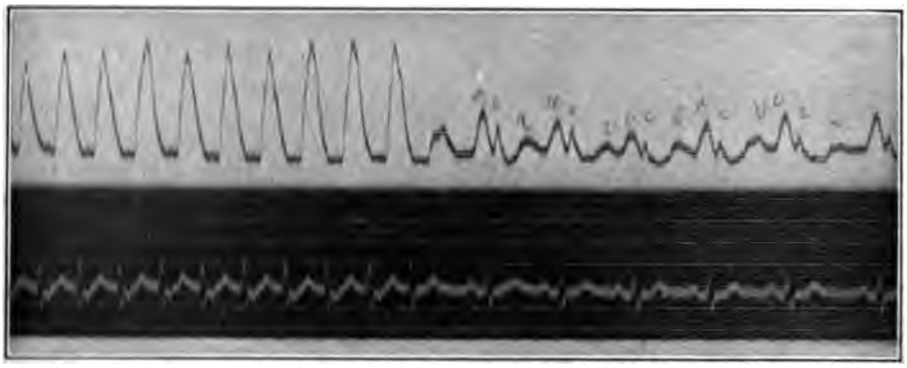


Fig 38. Paroxysmal Tachycardia with Transition to a Normal Rhythm. Note that during the Abnormal Rhythm the Inverted P Falls Directly after R of the Preceding Heart Cycle and that Since the Auricle Contracts during the Preceding Ventricular Systole, It Causes a Single Large Venous Wave. The Last R of the Tachycardia Is Not Followed by an Inverted P. The Next Auricular Contraction Originates in the Sinus Region (Upright P) and Thereafter the Rhythm Is Normal.

account of this delay, as well as on account of the rapid heart rate, it not infrequently happens that, during the paroxysm, the auricular contractions of one heart cycle coincide with the ventricular contractions of the preceding heart cycle. The contracting auricles, therefore, are unable to discharge their contents into the contracted ventricles but discharge the blood backward into the veins, thus producing a rather characteristic series of high waves on the venous pulse (Fig. 38).

Symptoms. The symptoms of paroxysmal tachycardia are due in part to the unusual heart rate. The patient is often conscious of his heart action, feels apprehensive and nervous, and is immediately relieved when the normal heart action is resumed. In prolonged paroxysms symptoms of cardiac insufficiency may develop, with breathlessness, diminution of

urine, and edema. The insufficient circulation of blood is due in part to the unfavorable effect of the extraordinarily rapid heart rate, and in part to the simultaneous contraction of auricles and ventricles, which leads to venous congestion and a poor blood supply to the ventricles.

Pathogenesis.—The pathogenesis of paroxysmal tachycardia is in a general way similar to the pathogenesis of extrasystoles. Experimentally, paroxysms have been produced by weak faradic stimulation of the auricles, by damage to the blood supply of the ventricles, etc. Paroxysms in man have been observed in nervous individuals as well as in those with evidence of organic heart disease, particularly coronary sclerosis. As with extrasystoles, the prognosis is, in general, more favorable in the young than in the old. The exciting cause of the paroxysms in man is frequently an unusual emotion, unusual exercise, a sudden change in posture, etc. The exciting cause is often so insignificant and the prognosis is often so favorable that paroxysmal tachycardia has been classed among the cardiac neuroses, a classification hardly in keeping with modern studies. The sudden termination of an attack of paroxysmal tachycardia often follows some such maneuver as a change in posture, a deep respiration, the sipping of cold liquids, the eructation of gas from the stomach, vomiting, pressure upon the vagus nerves in the neck, etc. Such maneuvers may be repeatedly effective in certain individuals, while in others they all fail. It is noteworthy that several of them involve vagus stimulation.

Auricular Flutter

In the condition known as auricular tachysystole or auricular flutter, the auricular rate is usually more rapid than in paroxysmal tachycardia, lying, as a rule, between 200 and 350 per minute. The auricular contractions are regular and coördinated, and they produce definite waves on both the jugular pulse and the electrocardiogram. The *P* waves are usually abnormal in one or more leads, indicating that the pacemaker has shifted from the sinus region to some other part of the auricle. Owing to the very rapid auricular rate, a partial block occurs between the auricles and ventricles, so that for every beat of the ventricles there are two or more beats of the auricles (Figs. 39 and 40). A two to one block is the most common in untreated cases. The ventricular rate, therefore, usually lies between 100 and 170 per minute and it is often perfectly regular. At times, however, the degree of block changes and sudden reductions of ventricular rate occur. Occasionally, the degree of block varies frequently, so that an irregular ventricular rhythm is produced, even though the auricles are beating regularly. Patients with flutter are, as a rule, rather sensitive to vagus pressure, which causes an abrupt drop in the ventricular rate owing to an increase in the block in the His bundle. When digitalis is given, it may also increase the block in the His bundle, and

thus cause a marked reduction of the ventricular rate. In other patients, digitalis may convert an auricular flutter into auricular fibrillation. This may disappear later with a resumption of the normal heart rhythm.

It will be seen that the essential difference between auricular flutter

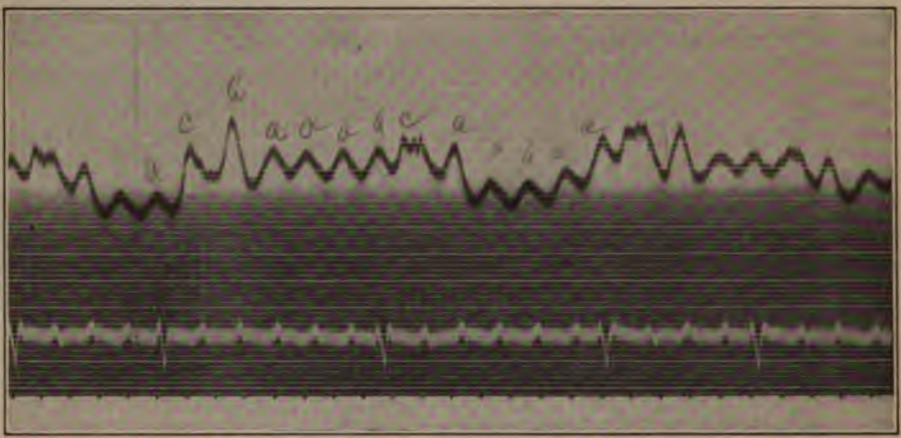


Fig. 39.—Auricular Flutter. Lead III. The Rapid Auricular Contractions Are Seen on the Venous Pulse and on the Electrocardiogram. The Ventricles Respond to the Fourth or Sixth Auricular Impulses.

and paroxysmal tachycardia is the more rapid rate of auricular contractions in the former condition. With this more rapid auricular rate the His bundle becomes unable to carry all the stimuli to the ventricles and blocks between auricles and ventricles result. From the clinical stand-

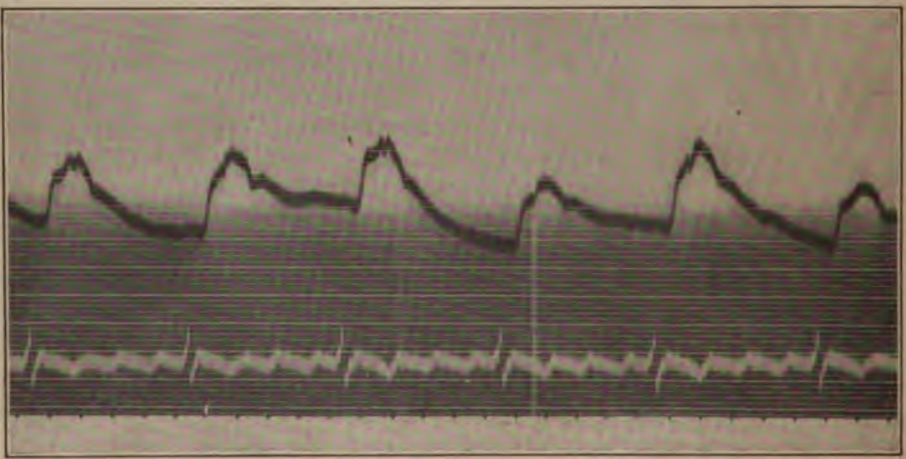


Fig. 40.—Auricular Flutter. Lead II. From the same Patient as Fig. 39. Shows the Abnormal Auricular Electric Complexes (Extra Sinus Origin of Beats). Also the Carotid Pulse.

point flutter is the more serious condition. Not only are the paroxysms more prolonged, but there is also a more definite tendency to pass into auricular fibrillation.

Auricular Fibrillation

Faradic stimulation of the auricles of the dog's heart usually causes a rapid and irregular series of incoördinated contractions of different parts of the muscle. In some cases coarse, wavelike motions are easily seen which involve a considerable part of the auricular muscle. This is the *coarse type of auricular fibrillation.* Under other conditions and particularly when the right vagus has been stimulated simultaneously, the auricles become dilated and their walls appear almost motionless. On close inspection, however, the smaller muscle bundles are seen to be executing very fine incoördinated movements. This is the *fine type of auricular fibrillation.* All transitions may occur between these two types.

Ventricular Arrhythmia.—When there is fibrillation of the auricles and impulses from these chambers still control the ventricular rhythm, the latter is always irregular. During fibrillation a large number of impulses are passing over the auricular muscle in various directions, and the upper end of the His bundle is bombarded by a very rapid and irregular succession of stimuli. The number of stimuli that succeed in reaching and stimulating the ventricles is governed mainly by the conductivity of the His bundle. When the conductivity is good, the ventricular rate reaches 100 per minute or more. When the conductivity of the bundle is diminished, as by vagus stimulation or after the administration of digitalis, the ventricular rate becomes slower. In either case, however, the stimuli come through irregularly and the ventricles show an absolute arrhythmia. No dominant regular rhythm, such as exists in partial heart block or extrasystoles, is discernible.

Venous Pulse.—The venous pulse of patients with auricular fibrillation usually shows no evidence of auricular activity. With each ventricular contraction there is a well marked *c* wave, which is followed by a more or less marked depression in the curve and this, in turn, by an unusually prominent *v* wave. The venous pulse is of a positive type, because the most marked upward movements occur during ventricular systole (Fig. 41). We have said that there is usually no evidence of auricular activity on the venous pulse. If the heart action is rapid, the waves of ventricular origin dominate the pulse, and finer waves which might possibly be produced by the auricles cannot be recognized. Only when the ventricular contractions are separated by long diastolic intervals is an opportunity given for small waves of auricular origin to become manifest. As a matter of fact, such waves are sometimes present on the jugular pulse and seem to be due to the auricular fibrillations (Fig. 42). In most cases, however, they are not seen. Only very rarely, as in a case recently reported

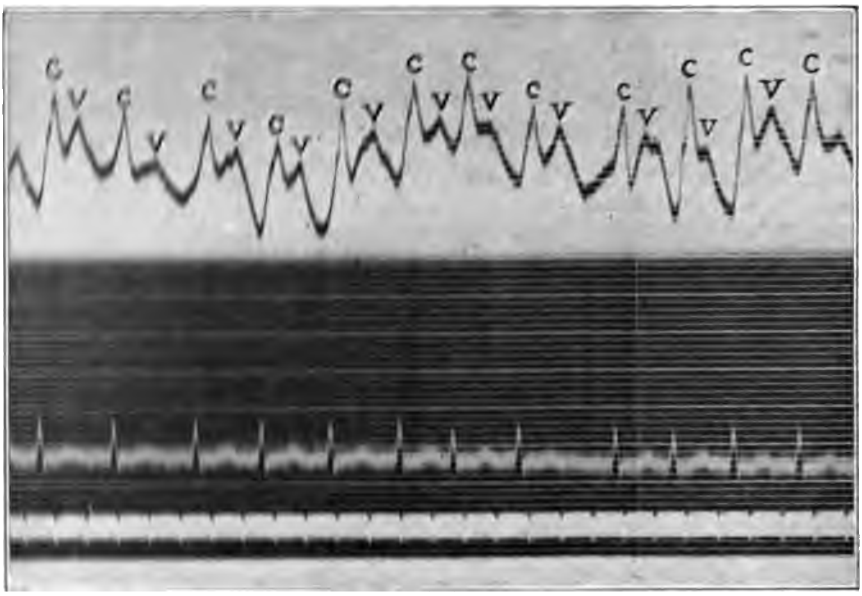
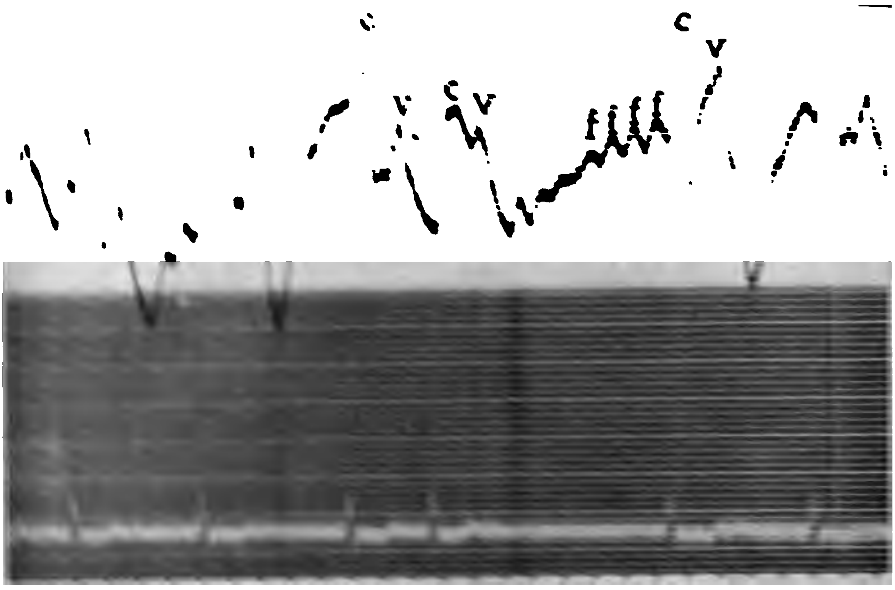


Fig. [illegible] Auricular Fibrillation with Rapid Ventricular Action. Note the Positive Venous [illegible] Waves. During the Longer Diastolic Pauses the Electric [illegible] Fibrillation Is Indicated by the Small Waves.



with Dr. Wilson, do these waves of auricular origin dominate the venous pulse (Fig. 43). These differences in the jugular pulse, in cases of auricular fibrillation, seem to be due to variations in the coarseness of the auricular movements. Auricular fibrillation in man is usually of a fine type, so that from the mechanical standpoint the auricles are practically paralyzed. Only occasionally are the fibrillations sufficiently coarse to cause definite venous waves.

Electrocardiograms and Mechanical Records.—Electrocardiograms taken from patients with auricular fibrillation show a succession of normal

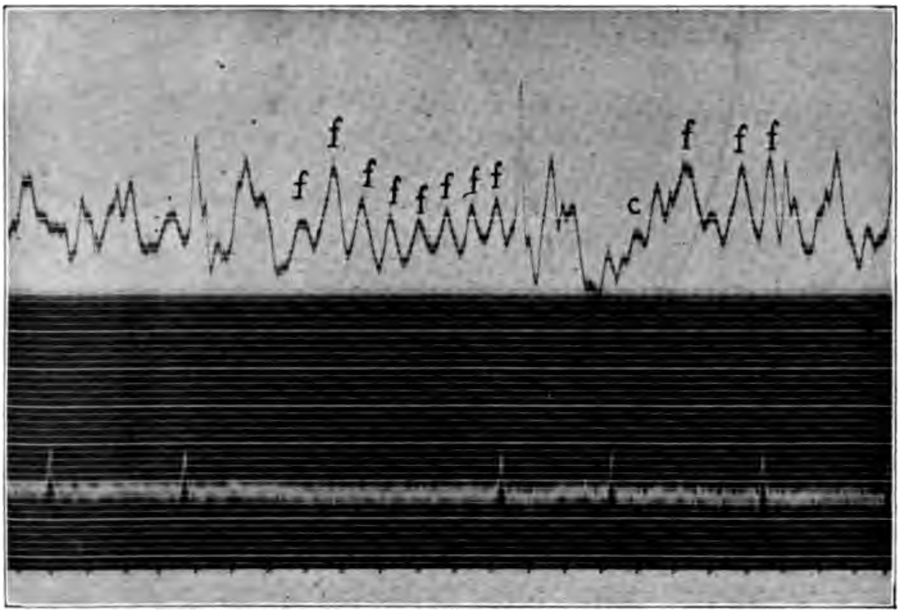


Fig. 43.—Coarse Auricular Fibrillation. Note the Large Venous Waves *f* Caused by the Auricular Activity. These Are Not Accompanied by the Definite Electrical Waves Seen in Auricular Flutter. They Are Irregular in Time. The Electrocardiogram Is Characteristic of Fibrillation.

ventricular complexes coming at irregular intervals. *P* waves are absent, but in their place there may frequently be observed small, rapid and irregular movements of the galvanometer string between the ventricular complexes. These are not present in all parts of the tracings, and they are coarser in some places than in others. The rate of these movements usually exceeds 380 per minute. These movements are due to the electric activity of the fibrillating auricles. When a comparison is made between these electric vibrations and the auricular venous waves occasionally recorded by mechanical means, it is found that, unlike the normal auricular systoles, there is no exact agreement between the two either in size or time (Fig. 43). The reason for this discrepancy lies in the fact that in auricular

fibrillation one is dealing with numerous interfering waves, and the summation of these may give mechanical effects which may differ from the electrical effects.

Pulse Deficit in Auricular Fibrillation

During auricular fibrillation with rapid ventricular rate, there is frequently a marked discrepancy between the number of ventricular contractions and the number of pulse waves which are felt or recorded at the wrist. Many ventricular systoles, and particularly those occurring during the more rapid heart action, either fail to open the semilunar valves, or expel quantities of blood that are too small to cause palpable arterial pulse waves. Such ventricular systoles are practically valueless from the mechanical standpoint, for they pump little or no blood into the aorta. At the same time, they cause an expenditure of ventricular energy, for we know that the isometric contraction of a muscle, such as occurs during the first part of ventricular systole, liberates considerable energy (page 3). The discrepancy between the number of ventricular systoles and the number of pulse beats palpable at the wrist has been called the "pulse deficit" by James and Hart. It indicates the number of ineffective ventricular contractions during auricular fibrillation.

Digitalis and Auricular Fibrillation

Of great practical importance is the fact that in auricular fibrillation, more than in any other condition, digitalis slows the heart rate. Therapeutic doses of this drug, when given to those with a normal sinus rhythm, rarely cause any appreciable reduction in the auricular rate, though occasionally, as we have seen, such doses may cause blocks between the auricles and ventricles. In auricular fibrillation, on the other hand, digitalis almost invariably slows the ventricular rate. This slowing is due to an increased block between the auricles and ventricles. We have seen that in auricular fibrillation the upper pole of the His bundle is constantly bombarded by numerous stimuli, and that the ventricular rhythm is determined by the number of these which succeed in reaching the ventricles. When the conductivity of the bundle is depressed by digitalis, the ventricles beat more slowly and often more regularly, even though the abnormal auricular activity continues. With a slower and more regular ventricular action, each ventricular contraction becomes mechanically effective and the pulse deficit tends to disappear. The great benefit which follows the use of digitalis in such cases is due in part to this cause, and in part to an improvement in the contractile power of the ventricles.

Permanent and Paroxysmal Fibrillation

Auricular fibrillation is, in most instances, a peculiarly constant irregularity, so much so, that it has been called the permanent irregularity

(P. irregularis perpetuus). Most patients coming under observation with auricular fibrillation show this condition on all subsequent examinations. Occasionally, however, even when fibrillation has persisted for a long period of time, it suddenly disappears and the normal cardiac mechanism is restored. Occasionally, also, patients are observed who show recurrent paroxysms of auricular fibrillation. These paroxysms may persist for minutes, hours, or days. They appear and disappear abruptly. Such paroxysms may be induced by exertion, excitement, sudden movements, straining at stool, etc. The cardiac mechanism in such paroxysms differs in no particular from that present in the permanent type of fibrillation. In questioning patients with a permanent irregularity, one obtains, not infrequently, a history which suggests that the irregularity was at first not permanent, but that it began with paroxysms of irregular heart action. Furthermore, patients who have paroxysmal fibrillation may ultimately develop a permanent irregularity, although sometimes this change does not occur for many years after the first paroxysm. It seems probable, therefore, that in many patients auricular fibrillation first appears in the form of paroxysms, and that these later become permanent.

Relation of Fibrillation to Ectopic Auricular Beats

Auricular extrasystoles, auricular tachycardias and auricular fibrillation are intimately related both experimentally and clinically. A single electrical stimulus applied to the auricle causes a single premature auricular beat or, occasionally, a succession of such beats. If the auricle be stimulated by a weak faradic current, rapid regular contractions, mostly of a coördinate character, may be produced. If the strength of the current is increased, the irregular incoördinated contractions of fibrillation occur. These may be fine or coarse. Stimulation of the right vagus nerve may convert a combination of fine fibrillation and rapid regular contractions into fine fibrillation (Robinson); or it may convert a coarse into a fine fibrillation. Certain drugs, such as physostigmin, may produce occasional or repeated auricular extrasystoles in small doses, and auricular fibrillation in large doses.

Clinically also, numerous transitions have been observed between auricular extrasystoles, paroxysmal tachycardia, auricular flutter and auricular fibrillation. Patients who suffer from attacks of paroxysmal tachycardia frequently show at other times auricular extrasystoles, and these are particularly numerous just before and just after the paroxysms. Auricular extrasystoles are also common after paroxysms of auricular fibrillation, and transitions between auricular flutter and auricular fibrillation are rather common. The administration of digitalis has frequently converted a flutter into a fibrillation. Finally, in a single patient, one may have, at one time, occasional auricular extrasystoles, at another time,

a rapid succession of extrasystoles (auricular tachycardia), and, at still another time, paroxysmal auricular fibrillation. It seems evident, therefore, that an intimate relationship exists between all these forms of auricular arrhythmia. The differences are quantitative rather than qualitative. At the one end of the series are the isolated auricular extrasystoles, and at the other auricular fibrillation. Between these two extremes lie the cases of auricular tachysystole, which produce the clinical conditions known as paroxysmal tachycardia and auricular flutter.

Pathogenesis of Auricular Fibrillation

Auricular fibrillation occurs most frequently in elderly patients in whom one may suspect poor nutrition of the heart muscle. It is also frequent in the later stages of mitral disease, where it is probably favored by the dilatation of the left auricle. It is fairly common in patients with chronic hypertension as well as in the later stages of thyroid disease, constituting a serious form of the "goiter heart."

From the intimate relationship that exists between auricular extrasystoles, auricular tachycardias and auricular fibrillation, it seems probable that all are produced by similar pathological changes. Experimentally, fibrillation may be produced by rapid electrical stimulation of the auricles and by drugs which seem to irritate the auricular muscle. Its occurrence is also favored by stimulation of the right vagus nerve.

Two General Hypotheses.—In order to explain the peculiar, incoordinated, wavy contractions that pass over the auricular muscle in all directions, two general hypotheses have been advanced. The first of these assumes that *abnormal stimuli are arising from numerous separate points within the auricular muscle*, and that the large number of contraction waves, thus initiated, interfere with each other in their passages over the muscle and produce fibrillation. It is well known, however, that fibrillation may result from the rapid stimulation of a single small area of the muscle, particularly when the right vagus nerve is stimulated simultaneously. There is here no reason to suppose that other regions of the auricle are initiating contractions. Furthermore, when fibrillation has once been started, the original point of stimulation may be removed and yet the fibrillation may persist for a time. It is evident, therefore, that fibrillation cannot be explained solely on the assumption of numerous stimuli to different parts of the muscle. An *impairment of conduction in the auricular muscle* plays a part in the pathogenesis of fibrillation. When a very rapid succession of contractions is initiated, the conductivity of the auricular muscle may become so depressed that the successive waves are not immediately carried to all parts of the auricles. In place of a rapid series of coördinated auricular contractions, there result wavelike contractions which spread in various directions from the point of primary

stimulation. It is the interference of these waves with one another, and the interference of individual waves with themselves, that produce the peculiar movements of fibrillation. Stimulation of the vagus nerve depresses conductivity in general. Such a depression in the auricular muscle would explain its effect in converting a coarse into a fine fibrillation. The observation that digitalis may convert an auricular flutter into auricular fibrillation is capable of a similar interpretation.

Pathological Anatomy.—The pathological anatomy of auricular fibrillation is not known. Changes in the region of the sino-auricular node have been described, but they appear to be neither constant nor characteristic. Indeed, from physiological considerations, one would hardly expect to find constant anatomical changes; for any area of the auricular muscle may be the original site of the numerous stimuli which presumably give rise to fibrillation. In discussing the pathogenesis of extrasystoles, it was pointed out that disease of any small section of muscle would be sufficient to initiate abnormal beats. The same is true of auricular fibrillation. Nevertheless the prognosis in fibrillation is much more serious than in extrasystoles. This is so partly because fibrillation is usually due to a more serious muscle lesion and partly because fibrillation disturbs the ventricular rhythm and causes the numerous ineffective systoles which constitute the pulse deficit. The effect of this abnormal heart action upon the efficiency of the heart is particularly evident in patients with paroxysmal fibrillation. Such patients may show evidence of cardiac insufficiency during their attacks, whereas they are free of symptoms when the heart is regular.

At autopsy, the auricles which have been the seat of fibrillation are often markedly dilated. Possibly this dilatation is a factor in producing the fibrillation, as may well happen in mitral stenosis. On the other hand, fibrillation itself favors dilatation, as is evident from animal experiments. In some patients with the permanently irregular pulse, however, the auricles are not dilated at autopsy. This fact was used by Mackenzie as an argument against the older view that this irregularity was due to auricular paralysis.

Ventricular Fibrillation

Experiments on the heart are often terminated by the unwelcome onset of ventricular fibrillation. This condition is often preceded by ventricular extrasystoles, which occur at first occasionally, and then in more rapid succession. The extrasystoles are succeeded by coarse, wavelike contractions, which spread rather slowly over the ventricles. These coarse, fibrillatory movements gradually become finer and finer until ultimately the ventricles become almost motionless, though still the seat of innumerable incoördinated contractions of the smaller muscle bundles. The steps in

the process indicate that, in the ventricles as in the auricles, there is a gradual transition from extrasystoles to coarse, and then to fine fibrillations.

Experimental Fibrillation.—Ventricular fibrillation has been produced experimentally by the same groups of agents that cause auricular fibrillations; viz., electrical stimulation, deficient blood supply and injection of toxic substances. Of particular interest from the clinical standpoint is the fact that ventricular fibrillation has been produced experimentally in cats by proper doses of chloroform. It is probable that sudden death during the early stages of chloroform anesthesia in man is due to this cause.

Cardiac Output.—During coarse ventricular fibrillation the pulse is weak and irregular, but as the fibrillation becomes finer no blood is expelled into the aorta. The finer type of ventricular fibrillation is, therefore, incompatible with life, and even the coarser type causes a serious impairment of the circulation. Electrocardiograms taken during ventricular fibrillation show a succession of wide, irregular excursions, similar to those which occur during ventricular extrasystoles. By the electrocardiograph, therefore, it should be relatively easy to recognize ventricular fibrillation in man.

Connection with Sudden Cardiac Death.—Nevertheless, we know little about its occurrence in man, probably because the condition promptly leads to death, and no opportunity is afforded for the taking of records. Although only a very few cases in man have been reported, it seems probable that ventricular fibrillation is a not infrequent cause of sudden cardiac death. We have already mentioned that it may be responsible for certain sudden deaths on the operating table, particularly during the early stages of chloroform anesthesia. Experimentally, occlusion of the coronary arteries may give rise to ventricular fibrillation, and it seems probable that certain sudden cardiac deaths in man during attacks of angina pectoris, or as a result of coronary disease, may be due to this cause. Sudden death is not infrequent in patients suffering from auricular fibrillation, and the view has been expressed that the fibrillation spreads from the auricles to the ventricles. This seems improbable, however, for Lewis has shown, that a narrow strip of conducting tissue is sufficient to prevent the spread of fibrillation from one portion of the auricular muscle to another.

Pulsus alternans

In the pulsus alternans the ventricles beat with perfect regularity but the pulse waves are alternately large and small. It frequently happens that, at the wrist, the smaller waves are retarded, being followed by a somewhat shorter interval than the larger waves. This is not due to any irregularity in the heart itself, but is caused by the fact that the smaller waves take a somewhat longer time to reach the wrist, partly because the

opening of the semilunar valves may be a little delayed, and partly because the propagation of the small wave in the arteries may be a little slower. Records of the ventricular action taken either mechanically at the apex, or by the electrocardiograph, show that the ventricular rate is perfectly regular (Fig. 44). No abnormality other than the size of the pulse waves has been discovered.

Varying Contractile Power of Left Ventricle.—The pulsus alternans appears to be due to variations in the contractile power of the left ventricle. After a relatively powerful systole, its power is not fully recovered by the time that the next stimulus reaches it and the succeeding contraction is weaker. After the weak systole, the ventricle accumulates greater contractile force and the next beat is more powerful, and so on. Whenever

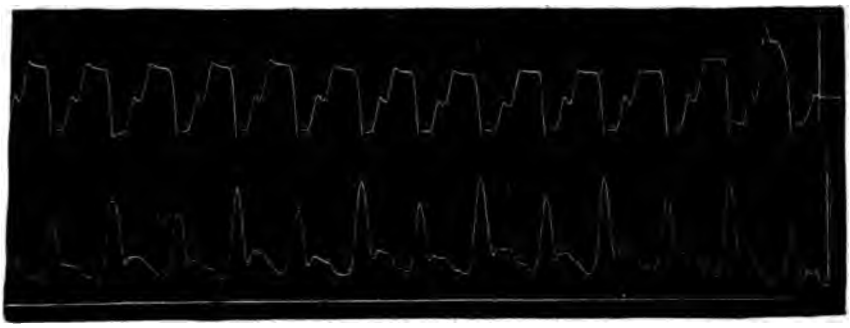


Fig. 44.—Pulsus alternans. Upper Tracing from the Apex. Lower from the Radial. Note the Alternation of Large and Small Beats. Venous Pulse Was Normal.

the heart rhythm is interrupted by an extrasystole the succeeding normal beat is unusually large. In patients who show a tendency to the occurrence of the pulsus alternans this large beat is commonly followed by a more pronounced alternation of large with small beats. Other than this the alternating pulse is usually quite constant from day to day.

The alternating pulse is encountered particularly in patients with high blood pressure and in those with myocardial weakness. The variations in the size of the pulse waves may be recognized on palpation or they may be recorded with a sphygmograph. They are often particularly evident when the systolic blood pressure is being taken, for as the pressure in the cuff about the arm is raised, the smaller beats disappear before the larger beats. The difference in systolic pressure of the two may amount to 20 or 40 mm. Hg. or more.

When the pulsus alternans is marked in patients with a normal blood pressure, it indicates a serious impairment in the contractile power of the ventricles and it is of serious omen. When it is barely recognizable, or when it occurs under the heavy load of a high blood pressure, the prognosis is somewhat less serious.

Heart Sounds and Heart Murmurs

Two principal heart sounds are heard with each cardiac revolution. The first occurs at the beginning of ventricular systole, and the second at the beginning of diastole (Fig. 45). The second sound, which is usually louder over the base of the heart, is produced by the vibrations which accompany and follow the closure of the aortic and pulmonary semilunar valves. The first sound, which is louder at the apex of the heart, is made up of two elements: first, the vibrations caused by the closure of the auriculoventricular valves; and, second, a muscle sound produced by the contraction of the ventricular wall.

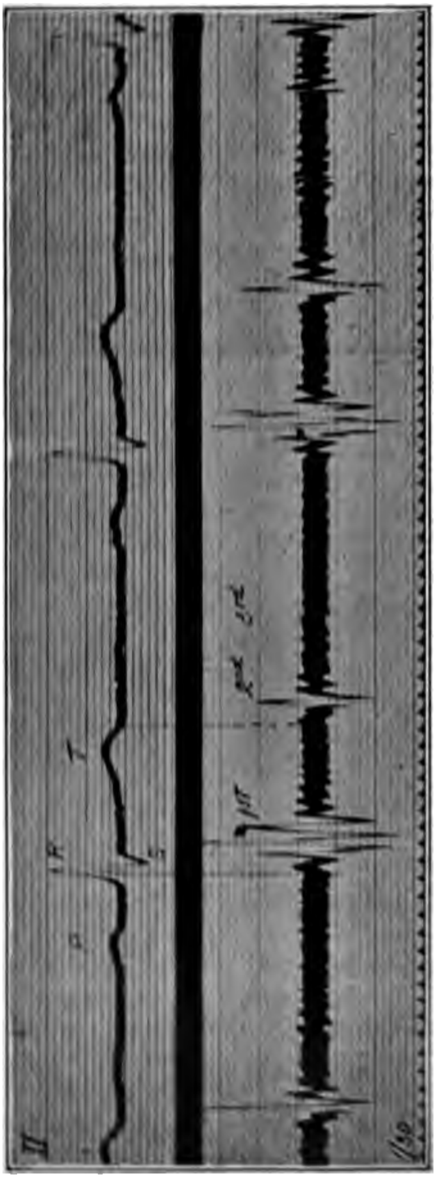


Fig. 45.—Electrical Records of Heart Sounds. The First and Second Sounds Are Well Marked, the Third Sound Indicated. (From Lewis, "Lectures on the Heart," published by Paul B. Hoeber.)

Changes in Loudness and Quality

The second sound, produced by the closure of the aortic semilunar valves, is best heard to the right of the sternum in the second intercostal space. At this point, the ascending aortic arch approaches the anterior chest wall. The second sound, produced by the closure of the pulmonary valves, is best heard in the second or third intercostal space to the left of the sternum. In young individuals the second sound is usually louder in the latter position, while in older individuals the reverse is the case (Cabot). An increase in intensity (accentuation) of either second sound may be produced by an increased pres-

sure in the corresponding arterial system. In the pulmonary congestion that accompanies mitral stenosis, for example, the second pulmonic sound is usually accentuated; whereas in chronic arterial hypertension the aortic second sound is usually loud. Accentuation of the second sound, and particularly a ringing quality, may also be due to sclerotic changes in the valves or the neighboring aorta. Such changes influence the character of the sound vibrations. Finally, the second sound becomes louder whenever the conduction of sound from its point of origin to the chest wall is favored by changes in the intervening tissues. In pulmonary tuberculosis, for example, a consolidation or retraction of the anterior edge of the left lung may cause a marked increase in the loudness of the second pulmonic sound.

Variations in the loudness and character of the first heart sound also occur, but their significance is less perfectly understood. That the sounds heard at the apex are influenced by the overlying cushion of lung seems obvious, and in pulmonary emphysema, for example, the heart sounds at the apex are often unusually feeble. A sharp "valvular" quality of the first sound is frequently associated with conditions in which the ventricular filling seems to be incomplete. This may be the explanation for the alteration in the quality of the first sound during rapid heart action and in conditions of low blood pressure. The peculiar first sound heard during certain ventricular extrasystoles may be due to the simultaneous contraction of auricles and ventricles, for Lewis has recorded loud first sounds during complete heart block at such times. The loud and "snapping" quality of the first sound in mitral stenosis may be due, in part, to an imperfect filling of the left ventricle. It is probably due, in part also, to changes in the sounds produced by the diseased mitral valves. When, as in chronic arterial hypertension or aortic insufficiency, the ventricle is hypertrophied and is contracting powerfully, the first sound often seems more prolonged and assumes a booming quality.

Split Sounds

Since each heart sound is composed of various elements, it is but natural to expect that, under pathological conditions, a lack of synchronism in these elements might lead to a splitting or reduplication of the heart sounds. Reduplication of the second sound occurs particularly when, as in mitral disease, the pressure in the pulmonary circuit is increased, and a prolongation of the systole of the right ventricle delays the closure of the pulmonary valves. Splitting of the first sound has also been described, but the mechanism of its production is less clear. The stimulus for ventricular contraction may certainly be interrupted in a primary branch of the His bundle, and it has been claimed that this may cause an audible interval between the first sounds produced on the two sides of the heart.

In other cases splitting of the first sound may be due to a dissociation between the valvular and muscular elements that produce it. The conditions here are by no means clear, and they require further study.

Accessory Heart Sounds

Even in normal individuals a third heart sound is not infrequently heard at the apex of the heart. This sound is faint and dull, and follows immediately after the second sound, so that it suggests an echo. Thayer observed such a third sound in over eighty per cent of individuals between the ages of 10 and 20 years. He found that it is less frequent in older individuals. This normal third sound is best heard when the individual is recumbent, and particularly when he is lying on the left side. It is louder just after the onset of expiration. This sound coincides in time with a wave which occurs on apex tracings shortly after the abrupt fall that marks the end of systole. A corresponding wave, the *h* wave, may occur on the jugular pulse (Figs. 19 and 24). The third sound, therefore, occurs during early diastole just after the first rush of blood into the ventricles, and it is associated with waves on the apex and venous tracing which indicate that the first rush has been completed. Hirschfelder suggests that, owing to an elastic recoil of the ventricular walls immediately after this primary filling, the auriculoventricular valves are snapped together with sufficient force to produce the third sound.

Gallop Rhythm

In gallop rhythm, three sounds, instead of two, are heard with each heart cycle. If we omit from consideration the occurrence of split sounds, the extra sound heard in gallop rhythm usually occurs during diastole. It may precede the normal first sound (presystolic gallop rhythm) or it may follow the second sound (protodiastolic gallop rhythm). If diastole is short, the relation of the extra sound to the preceding and succeeding systoles is difficult to determine.

Protodiastolic Gallop Rhythm.—The protodiastolic type of gallop rhythm is probably due to an increase in the intensity of the normal third sound. Since this sound is associated with changes which occur just after the first rush of blood into the ventricle, one would expect it to be louder than usual, whenever the rush of blood is increased by a heightened venous pressure in the pulmonary or systemic circuit. The occurrence of this sound in mitral insufficiency and in cardiac insufficiency secondary to arterial hypertension may be readily explained in this manner. So, too, the gallop rhythm observed in patients with adherent pericardium may be due to a sudden ventricular diastole caused by the pull of surrounding adhesions. In mitral stenosis a protodiastolic gallop rhythm is not un-

common, but it evidently cannot be caused by a sudden ventricular filling. Its mode of causation is at present uncertain, though in some cases it may represent an aborted murmur in early diastole..

Presystolic Gallop Rhythm.—In the presystolic type of gallop rhythm, the accessory sound is attributed to an audible auricular contraction. That auricular contractions may produce audible sounds has been demonstrated conclusively in patients with complete heart block. In such patients a faint sound accompanying each auricular contraction may be heard and recorded (Fig. 46). Normally, the auricular sounds are either too faint or too fused with the first heart sound to be clearly distinguished. One

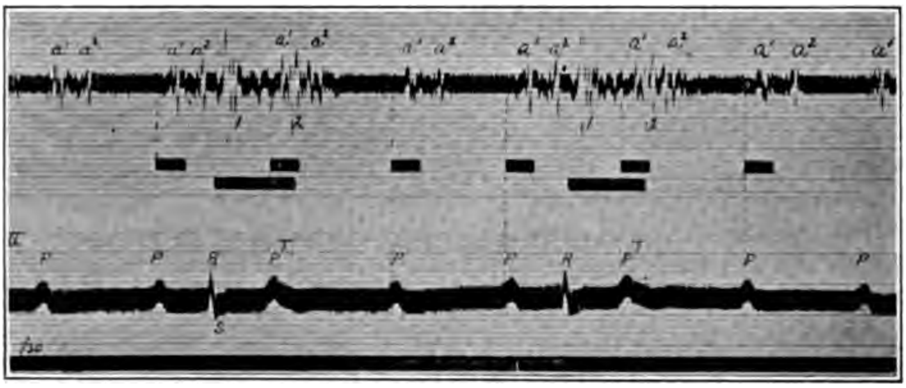


Fig. 46.—A Record of Auricular Sounds in a Case of Complete Heart Block. (From Lewis, "Lectures on the Heart," published by Paul B. Hoeber.)

would expect that under pathological conditions the auricular sounds might become audible, because the interval separating them from the first sound was increased. As a matter of fact, the interval between the auricular and the ventricular systoles is increased in some cases of presystolic gallop rhythm. This is not always the case, however, and where presystolic gallop rhythm occurs in patients with a normal *As-Vs* interval, it appears to be due to an unusually loud auricular sound, which is probably caused by an increase in the force of the auricular contractions. As a matter of fact, presystolic gallop rhythm is often found when there is an hypertrophy of the auricles. Since the conditions which lead to hypertrophy of the auricles are, in many ways, identical with those which increase the rush of blood into the ventricles during early diastole, it is to be expected that presystolic and protodiastolic types of gallop rhythm would tend to occur in the same classes of disease. Such seem indeed to be the case. Furthermore, Müller, and also Potain, have described instances in which a gallop rhythm changed from one type to the other in the same individual.

Valvular Murmurs

If water be allowed to flow through a rubber tube that has been attached to a faucet, a constriction of the tube will, under proper conditions, cause the tube to vibrate. These vibrations are more readily produced when the flow through the tube is rapid. If the constriction be gradually produced, no vibrations occur at the onset. As the constriction increases, the vibrations appear and increase in intensity up to a certain maximum, after which they diminish and finally disappear as the flow of water through the constriction is checked. The vibrations thus produced are most marked beyond the point of constriction; being, so to speak, transmitted in the direction of the current. In valvular heart disease, the blood also flows through narrow orifices, and it causes vibrations in the valves and adjacent structures similar to those produced in the rubber tube. When these vibrations are felt they are spoken of as thrills, when heard they are called murmurs. Rapid vibrations produce high-pitched murmurs, which are not readily felt. Slow vibrations produce low-pitched murmurs and palpable thrills.

Neither thrills nor murmurs accompany the normal heart action. When the valves close, the closure is so perfect that little if any blood escapes. When the valves open, the valvular orifices are not sufficiently narrow to give rise to vibrations. Murmurs may be produced either by a leak in a valve during its time of closure (insufficiency) or by an abnormal narrowing of an orifice which obstructs the onflowing current of blood (stenosis). The time in the heart cycle at which murmurs occur is therefore obvious. During ventricular systole the semilunar valves are open and the auriculoventricular valves are closed. Systolic valvular murmurs may, therefore, be produced either by a stenosis at a semilunar orifice, or by an insufficiency of the auriculoventricular valves. Similarly during diastole, the semilunar valves are closed and the auriculoventricular valves are open. A diastolic murmur may then be produced either by an insufficiency of the former or by a stenosis of the latter.

Cardiac murmurs, like the vibrations produced in a rubber tube, tend to be transmitted in the direction of the current that is producing the murmur. Thus the murmur of aortic stenosis is usually transmitted to the vessels of the neck, whereas the murmur of aortic insufficiency is transmitted in the opposite direction, and is usually best heard to the left of the sternum, along the left border of the precordium and at the apex.

The loudness of a valvular murmur is determined by various factors, chief among which are the size of the orifice, the rate at which the blood passed through it, and the condition of the surrounding structures. No definite relation exists between the loudness of a murmur and the seriousness of the lesion. In aortic stenosis, the murmur is usually a loud one, and will become louder, other things being equal, as the stenosis increases.

In insufficiencies, on the other hand, a very wide opening may ultimately lessen the murmur. Furthermore, the retarded circulation of cardiac insufficiency tends to reduce the loudness of all murmurs. It is, therefore, evident that, in the most serious lesions of all, the murmurs may not be loud and that they may become louder as compensation is established.

In Mitral Stenosis.—Of all valvular lesions mitral stenosis is the one which produces the most variable murmurs. This murmur not only varies in loudness from time to time, but it may occupy varying positions in diastole. The position in diastole depends largely upon the rate at which blood flows through the stenosed orifice. Normally, as we have seen, the blood enters the ventricle most rapidly in early diastole, and, if the heart rate be slow, the ventricular filling may be practically completed by the middle of diastole. The auricular contraction sends but an insignificant amount of blood into the ventricle. In mitral stenosis, on the other hand, the left auricle may play an important compensatory part in forcing blood through the stenosed orifice, so that in this condition the rate of ventricular filling is most rapid at the beginning and at the end of diastole (Fig. 16). These are indeed the common sites of the mitral stenosis murmur. When the auricle is active, the murmur is usually heard in presystole, i. e., at the time of the auricular contraction. It may begin sometime before this, or it may occupy the whole of diastole, but the presystolic portion of the murmur is practically always present. If the relation between auricular and ventricular contractions be disturbed, the murmur changes. Thus with a lengthened *As-Vs* interval the murmur accompanying auricular systole may cease before the onset of the first heart sound, and in heart block the isolated auricular contractions may produce isolated murmurs. Most important of all, however, is the change in the murmur of mitral stenosis which takes place when the auricles cease to contract during auricular fibrillation. If the diastolic pauses are short, the murmur may still fill diastole; but when the diastolic pauses are long, the murmur begins shortly after

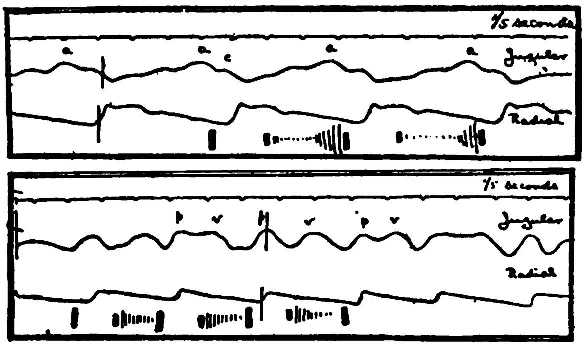


Fig. 47.—Change in the Murmur of Mitral Stenosis during Paroxysmal Auricular Fibrillation. During the Regular Heart Action (above) when the Auricles Were Beating Normally the Murmur Was Loudest just before the First Sound (Presystolic Murmur). When the Auricles Were Fibrillating the Murmur Was Loudest just after the Second Sound and the Presystolic Accentuation Was Lost. (From Hewlett, Jour. Am. Med. Assn.)

the second sound and ceases before the end of diastole. The presystolic accentuation disappears with the cessation of normal auricular contractions (Fig. 47).

Accidental Murmurs

Cardiac murmurs not infrequently occur when there is no anatomical disease of the heart valves. In relative insufficiencies of the valves, regurgitation occurs because the musculomembranous ring to which they are attached is abnormally wide. It is evident that, under such circumstances, the mechanism of murmur production and the effects produced on the circulation will differ in no essential way from the effects produced by insufficiencies that are caused by valvular disease. The murmur of a relative mitral insufficiency may disappear as compensation is reëstablished and the dilatation of the left ventricle lessens.

In the so-called accidental murmurs, on the other hand, there is, so far as we know, no regurgitation and no evident stenosis. Murmurs of this type are relatively frequent in Graves's disease, in the anemias, and in infections; but they may also occur in other pathological conditions and even in normal individuals. Accidental murmurs are usually systolic in time, and they are usually louder over the pulmonary area than at the apex of the heart. They rarely cause a disappearance of the first heart sound, and they may be heard only during a limited portion of systole. A certain number of these murmurs doubtlessly arise not in the heart, but in the lungs, and are due to movements of the air caused by the cardiac contractions. Such cardiorespiratory murmurs often vary considerably with the different phases of respiration, and they may disappear at certain phases. It seems improbable, however, that cardiorespiratory murmurs make up the sum total of what are known as accidental murmurs; but the cause or causes for the remainder is still obscure. Changes in the speed of the blood current may play a part, particularly when, as in anemias, the rate of blood flow is believed to be increased. Lüthje has suggested that a functional stenosis of the pulmonary artery may be instrumental in their production.

Some Manifestations of Heart Disease

Cyanosis

The deep purple color of cyanosis is usually most evident on the mucous membranes, the finger nails, and certain portions of the skin, particularly the hands, the feet, and the cheeks. The change in color is due to changes in the hemoglobin. These changes may be of various kinds. In poisoning by potassium chlorate or acetanilid, as well as in pneumonia, a conversion of hemoglobin into the methemoglobin may give rise to cyan-

osis. The principal cause of the cyanosis associated with heart disease is an unusual reduction of the oxyhemoglobin present in the blood to hemoglobin. Any slowing of the blood stream favors the production of cyanosis, owing to the greater reduction of oxyhemoglobin that occurs in order to furnish the requisite amount of oxygen to the tissues. The degree and distribution of cyanosis is, therefore, influenced by the rate of blood flow through the different parts of the body. Thus the cyanosis of the hands and feet that follows the exposure of normal individuals to cold is a local cyanosis, and is dependent upon the very slow rate of blood flow through the extremities produced by cold. Cyanosis also depends upon the degree of filling of the superficial capillaries and venules. Exposure of the hands to cold may cause either a white or a cyanotic skin. In both cases, the blood flow through the extremity is very slow and the returning blood is of an unusually venous character. The difference in color depends upon differences in the dilatation of the superficial capillaries and venules. The hands are white when these vessels are constricted, blue when they are dilated. A dilatation of the superficial veins and capillaries does not necessarily increase the blood flow through the hands, for the arterioles which govern this flow may remain constricted even though the venules are dilated. It is obvious, therefore, that dilatation of the superficial capillaries and venules plays an important part in the production of cyanosis. For this reason those portions of skin, such as the cheeks, that normally show a pink color, are the regions that become very blue when there is a general cyanosis. Furthermore, cyanosis is particularly marked when there is a mechanical venous obstruction, for this not only slows the blood current, but tends to dilate the superficial venules.

The remarkable cyanosis that occurs in congenital heart disease is often associated with relatively few other signs of cardiac insufficiency. The cause of this cyanosis is not certain. One is tempted to assume that the defects, so common between the two sides of the heart, allow an escape of venous blood directly into the systemic circulation with a short circuiting of the lungs. While such a short circuit may occur and is favored by the common hypertrophy of the right ventricle, nevertheless, it can hardly be the rule, for the pressure on the left side of the heart is probably always higher than the pressure on the right. Under such circumstances, any deviation of blood would tend to be from the left to the right heart, rather than the reverse. One important factor in the production of cyanosis in congenital heart disease is a stasis in the systemic veins produced by the increased strain on the right side of the heart. In the later stages of pulmonary emphysema and in sclerosis of the pulmonary artery, extreme cyanosis is also common, and here again it is due in part to a weakness of the right heart.

Most forms of extreme cyanosis are associated with a definite increase in the number of red cells per cubic millimeter (see Polycythemia). In

certain cases this is a result, rather than a cause, of the unusual reduction of oxyhemoglobin to hemoglobin.

Cardiac Dyspnea

The dyspnea of heart disease is characterized by the fact that it becomes much worse on exertion, and that in advanced cases it is worse when the patient is recumbent than when he sits up. Cardiac dyspnea depends in part upon pulmonary congestion, and it is an early symptom in those forms of heart disease which, like mitral stenosis, cause pulmonary congestion. Cardiac dyspnea depends, furthermore, upon slowing of the blood stream and venous congestion. Its pathogenesis is still obscure, and it will be discussed more fully in the chapter on disturbances of the respiration.

Cardiac Edema

The edema of heart disease depends mainly upon stasis of the blood in the systemic veins. The relation to stasis, however, is not a simple one, for some patients with marked cyanosis or with marked swelling of the liver show little or no edema, whereas others with edema show little other evidence of stasis.

Local and General Circulatory Factors.—Of local circulatory factors that lead to edema, slowing of the blood stream appears to be relatively unimportant, for we know that the obstruction of an artery may produce considerable slowing of the local blood flow without producing edema. Extensive obstruction of the veins, on the other hand, not infrequently leads to edema. This has been demonstrated experimentally, and it is also a familiar clinical observation. The increased venous and capillary pressure leads to an excessive transudate from the capillaries, and the slow blood stream interferes with that absorption of lymph which normally takes place by way of the blood vessels. Edema also depends upon the condition of the lymph circulation, for this normally removes a portion of the fluids that leave the blood vessels. Any compression or obstruction of the lymph vessels may, therefore, contribute to a stasis of fluids in the tissues. Finally, edema develops more readily in loose tissues where the tension in the tissues is low.

In heart disease, the venous congestion and the slow blood stream reproduce conditions which are similar to those present in local venous obstruction. Since the venous and capillary pressures are highest in the dependent parts of the body, the edema of cardiac disease ordinarily occurs in these dependent parts. When the patient is on his feet the ankles are first affected and this is followed later by edema of the legs, genitalia and abdomen. When the patient lies down, the edema tends to diminish in the legs and to increase in the dependent portions of the back.

The concentration of the blood in cardiac edema may remain within the normal limits. In some cases, however, the blood becomes dilute just as it is in true nephritic edema (page 434), while with the disappearance of the edema the blood concentration returns to the normal. This dilute condition of the blood probably depends upon changes in renal function caused by a chronic passive congestion of the kidneys. When present, it is a contributing factor in the production of cardiac edema.

Pulmonary Edema

Pulmonary edema may be due to a variety of causes. In one group of cases, the edema is associated with infection of the lungs. Thus pneumonia may be ushered in with the symptoms of pulmonary edema. The importance of this infectious form of edema has been insisted on particularly by Sahli, and it is a not infrequent secondary or terminal event in chronic diseases. In another group of cases, abundant serous expectoration follows the withdrawal of fluid from the pleural cavity, and is due to the sudden circulatory changes in the lung that has suddenly expanded. In a third group, the edema is caused by drugs, such as pilocarpin.

Mechanical Factors.—It has long been known that edema of the lungs is frequent in those suffering from cardiac disease, and particularly in those with chronic arterial hypertension, nephritis, or coronary disease. In such patients, the edema may occur as a *terminal* event or it may recur in a *paroxysmal* form. The exact nature of the pulmonary edema which occurs in renal, cardiac, or vascular disease has been much debated, and it has been variously attributed to changes in the quality of the blood, damage to the pulmonary vessels and infection. While these factors undoubtedly may contribute to the etiology of pulmonary edema, the part played by mechanical changes in the pulmonary circulation is of particular interest, and they seem to play a predominant rôle in causing the paroxysmal type of the disease. According to the theory of Cohnheim and Welch, pulmonary edema results from a disproportion between the working power of the left and the right ventricles of such a character, that the left side of the heart is unable to expel the blood pumped by the right into the lungs. Some blood always collects in the lungs as a result of weakness of the left ventricle, but ordinarily this is not excessive, for the increased pressure in the pulmonary veins increases the filling of the left ventricle and improves its contractile powers, so that its output ultimately keeps pace with the output from the right side of the heart (page 8). In the condition which we are now describing, however, the weakness of the left ventricle causes such a marked rise in pulmonary pressure, that fluid escapes rapidly from the vessels into the air spaces. Mechanical edemas of this type have been produced experimentally by ligation of the upper thoracic aorta of rabbits, by obstructing the mitral orifice, and by ligating

the left coronary artery so as to cause a sudden weakness of the left ventricle. Clinically, paroxysmal edemas of the lungs are most frequently associated with conditions which throw an excessive strain on the left ventricle, such as aortic insufficiency, coronary sclerosis and chronic arterial hypertension. The view that a sudden and marked insufficiency of the left ventricle may produce one type of pulmonary edema is, therefore, in full accord with experimental and clinical observations.

Cardiac Sensations

Palpitation

A normal individual is rarely conscious of his heart's action. After exercise or during emotional disturbances he may feel a throbbing sense of palpitation, but, for the most part, the cardiac movements produce no afferent impulses which rise to the level of consciousness. Even the unusually large contractions of aortic insufficiency, or the extreme ventricular irregularity of auricular fibrillation, may cause no disturbing cardiac sensations.

Throbbing sensations produced by the heart action are experienced most frequently by patients who are in other ways nervous. While this heightened consciousness of impulses coming from the viscera is in general a factor in most cases of palpitation, nevertheless disturbing sensations arising from the heart are at times associated with more or less evident changes in the heart's action. For example, with extrasystoles the patient may complain that he feels the heart stop or that it thumps, either with the extrasystole or with the large ventricular contraction that immediately follows the intermission. During paroxysms of auricular fibrillation unpleasant sensations of cardiac throbbing and cardiac irregularity may be present. When the fibrillation becomes permanent these sensations tend to disappear, apparently because a continuation of the irregularity permits the patient to grow accustomed to the unusual nervous impulses coming from the heart. Wilson has recently observed a patient in whom palpitation recurred whenever there was a simultaneous contraction of ventricles and auricles, owing to a transference of the pacemaker to the nodal tissues (Fig. 32). Such simultaneous contractions occur not infrequently in paroxysmal tachycardia (Fig. 38), they probably play a part in causing the palpitation which is so common in this condition. In such cases, the unusual venous pulsations, caused by the fact that the auricles contract when the auriculoventricular valves are closed, appear to be the immediate cause of the abnormal sensations.

In a certain number of conditions, therefore, abnormal cardiac sensations are associated with demonstrable changes in the heart's activities. In many cases of palpitation, however, examination of the heart fails to

reveal any definite abnormality. One frequently gets the impression that the heart is "overacting," the apex beat being more sudden and violent, the rate somewhat rapid, and the first sound sharp in character. Conclusive objective evidence of such changes in the cardiac activities has not as yet been furnished; and, for the present, we must attribute many cases of palpitation to a heightened consciousness of the cardiac activity, rather than to any definite change in the cardiac movements.

Cardiac Pain

The heart, like many other viscera, is insensitive to tactile stimuli. Nevertheless, it is capable of giving rise to pain. Severe pain originating in the heart is always described as angina pectoris; but since all grades of transition occur between the severest paroxysms of angina and mild cardiac pains, the term angina pectoris may also denote any pain of cardiac origin. The character of such pain varies. There may be a feeling of great oppression hardly to be described as pain, or there may be a sensation of great weight upon the thoracic wall, or a feeling that the heart is being compressed in a vise, or, finally, the pain may be of a sharp, stabbing or tearing character. Cardiac pain is localized most commonly in the region of the heart itself, but it frequently extends to other parts of the thorax or to the inner side of the left arm. Less commonly, it radiates to the right arm, the neck, the back, the abdomen, or even the legs.

During or after an attack of cardiac pain, the patient may complain of numbness or tingling in the skin covering the precordium, the inner side of the left arm, or other regions affected by the pain. Objective sensory disturbances, and particularly a hypersensitiveness to painful stimuli, may also be demonstrated in these regions. Occasionally, also, the patient complains of muscular weakness or cramps in the affected arm or hand. Mackenzie attributes the sense of thoracic constriction to a spasm of the intercostal muscles, which is analogous to the spasm of abdominal muscles in diseases affecting the organs lying in that cavity.

Referred Pain and Other Disturbances.—The pain of angina pectoris is, therefore, felt not only in the region of the heart itself, but in distant parts of the body, and, furthermore, it may be associated with sensory as well as motor disturbances. An explanation for these phenomena, as well as for "referred" pains in general, is found in the work of Henry Head and James Mackenzie. These authors have pointed out that the regions of referred pain, cutaneous sense changes and muscle spasm or weakness are usually innervated from the same segments of the spinal cord, as is the organ which is the seat of disease. According to their hypothesis, the abnormal stimuli that come from a diseased viscus irritate the spinal cord, particularly at the level where they enter. This irritation of the cord leads, on the one hand, to conscious sensations, which are referred by the

brain to the exterior segments of the body innervated by the irritated portions of the cord. On the other hand, the irritation of the cord may lead to demonstrable sensory and motor changes in the skin and muscles innervated by the affected segments. The commonest site of cardiac pain corresponds to the peripheral distribution of the eighth cervical to the fourth dorsal spinal segments. These, as will be seen from Figure 48, innervate the skin of the precordium as well as a band that extends to the axilla, and from here down the inner aspect of the arm and forearm to the ulnar side of the hand. Afferent impulses from the heart are believed to enter this region of the cord and thus cause the characteristic distribution of pain. Unusual distributions of pain, as to the neck, the head or other parts of the body, may be explained partly as being due to a more extensive spread of the irritation within the spinal cord, and partly as being due to a stimulation of afferent cardiac fibers, which run in the vagus or depressor nerves to the region of the medulla oblongata.

Fig. 48.—Usual Distribution of the Pain and Sensory Disturbances in Angina pectoris. Corresponds to about the Distribution of the Eighth Cervical to the Fourth Dorsal Spinal Segments. (Modified from Mackenzie, "Diseases of the Heart," published by Oxford University Press.)

Pathogenesis.—What causes the afferent impulses which lead to the pains of cardiac disease? Patients who die of angina pectoris most frequently show at autopsy a sclerosis or obstruction of the coronary arteries. Disease of the first part of the aorta with aortic insufficiency is also common. Severe attacks of cardiac pain may also be due to the toxic effects of nicotin, or caffein, or to an acute cardiac strain owing to violent muscular exertion.

The exact manner in which these causes produce the pain is still unsettled. Several hypotheses have been advanced. According to the one most commonly held the pain is due to an *inadequate supply of blood* to the heart. It has been compared to the pains experienced by those who suffer from narrowing of the arteries in the lower extremities. Such patients may be comfortable so long as no exercise is taken, but shortly after they begin to walk they are seized with pains and weakness in the legs, which only disappear if the patient rests (intermittent claudication). The blood supply to the legs, which was sufficient for the resting needs of the

extremity, became insufficient during exercise, and the insufficient circulation caused the pain. The analogy to cardiac pain which is usually induced or made worse by extra work on the part of the heart is obvious. This inadequacy of the blood supply in the heart, as in the leg, may be due either to organic disease of the local arteries, or to their functional spasm.

Others have attributed the pains of cardiac diseases to an *acute dilatation of the heart muscle* and the efforts made by the heart to overcome the increasing dilatation. An analogy may here be drawn to the colicky pains excited when a hollow viscus, such as the stomach, the intestines, the bile passages or the ureter, is rapidly distended by material that collects behind an obstruction and contracts violently in the endeavor to overcome the obstruction.

Blood Pressure and Angina pectoris.—The relation of increased blood pressure to the pains of angina pectoris is interesting and important. In some, but not in all patients, attacks of angina are accompanied by a rise, and often a marked rise, in the systemic blood pressure. When the blood pressure is reduced by the administration of vasodilators the pains usually become much less severe. It is obvious that the rise of blood pressure tends to increase the strain on the heart; yet the exact relation between the acute hypertension and the pain is not definitely known. It is possible, for example, that the rise of blood pressure is caused by the pain. It is possible that a general vasoconstriction is associated with a constriction of the coronary arteries, and that the latter is the immediate cause of the anginal pains, owing to a reduction in the blood supply to the heart muscle. It is possible, finally, that a primary constriction of the peripheral arterioles causes the rise of blood pressure, and that the rise of pressure produces the paroxysm by increasing the dilatation of the heart muscle.

In certain patients no rise in the general blood pressure accompanies the attacks of angina pectoris. In such cases the use of vasodilators is less successful than when the attacks are associated with hypertension. Attacks of this type appear to be relatively serious in character.

The Blood Vessels

Physiological Considerations

The blood vessels of the systemic circulation form a continuous and closed set of tubes that lead from the aortic semilunar valves to the openings of the venæ cavæ into the right auricle. The vessels of the pulmonary circulation conduct the blood in a similar manner from the right ventricle to the left auricle. Into the aorta and pulmonary artery the

ventricles periodically discharge a portion of their contents, thus producing the intermittent changes in pressure and the intermittent movements of blood that constitute the arterial pulse. Blood does not flow freely through the fine capillaries and smaller arterioles. This peripheral resistance tends to hold back the blood to a greater or lesser extent in the larger arteries, and thus causes the high arterial pressure.

In the pulmonary circuit the vessels usually play but a passive rôle. Vasomotor nerves to these vessels have been demonstrated, but their action is insignificant when compared with the effects produced by changes in the output from the two sides of the heart. Only extensive disease of the lungs or of the pulmonary vessels influences the circulation as a whole. In the systemic circuit, on the other hand, changes in the caliber of the vessels play an important rôle in controlling the height of the blood pressure and in distributing blood to the various organs.

Owing to the resistance encountered in the blood vessels there is a progressive fall of pressure from the arterial to the venous side of each circuit. This fall is most marked where the resistance is greatest. According to Starling, the following indicate the usual mean pressures in different parts of the systemic circulation:

Large arteries (e. g., carotid)........	90	mm.	mercury
Medium-sized arteries (e. g., radial)...	85	"	"
Capillaries, about	15-40	"	"
Small veins (of the hand)..........	9	"	"

It is evident that the main fall of pressure takes place between the medium-sized arteries and the veins. A part of this fall takes place in the capillaries, but the smaller arterioles also interpose a considerable amount of resistance to the flow of blood, and from the physiological standpoint they are of dominant importance owing to the fact that they, more than any other part of the vascular system, are subject to marked changes in caliber.

Mean Arterial Pressure.—The mean arterial pressure is determined by two factors: the rapidity with which the blood is expelled from the heart, and the ease with which it escapes from the arteries. The former is determined by the number of cardiac contractions in the unit of time and by the output at each contraction. The latter is determined by the viscosity of the blood and by the size of the arterioles and capillaries throughout the body. The blood pressure may remain constant despite marked variations in the cardiac output, for there may be equally marked changes in the peripheral resistance. Thus Tigerstedt records experiments in which, with a blood pressure of from 91 to 100 mm. of mercury, the output from the heart varied in maximo from 9 c.c. to 149 c.c. per minute per kilo of body weight. Conversely, the minute output may remain practically constant even though there are marked variations in the blood

pressure; and, again, Tigerstedt records an experiment in which the blood pressure varied from 58 to 112 mm. of mercury, while the minute volume remained practically constant (130 to 149 c.c.). It is obvious that no conclusion as to the cardiac output can be drawn from the height of the mean blood pressure.

Arteriolar Contraction.—Of no little interest is the question as to whether the blood pressure is more commonly influenced by the cardiac output or by the peripheral resistance in the arterioles. While this question cannot receive a general answer and must be studied in each case, nevertheless it is interesting to recall Tigerstedt's conclusion. "It seems, from all of the experiments bearing upon this question, that the blood pressure, although equally dependent upon the peripheral resistance and the minute volume from the heart, is nevertheless governed above all by the degree of contraction of the vessels at the moment. If the vessels are markedly dilated, then the heart ultimately cannot receive sufficient blood to sustain a high blood pressure. On the other hand, one may say that there is no limit for increases of resistance. During sufficiently strong stimulation of the vasomotor nerves the lumina of the vessels practically disappear, and with a marked resistance a very small output from the heart suffices to maintain a high blood pressure."

Not only do the arterioles play an important rôle in regulating the systemic blood pressure, but the degree of their contraction governs the local blood flow to particular vascular areas. When the arterioles to a given organ dilate, more blood flows through this organ. Only in the case of the brain does the normal blood supply appear to depend more on the height of the blood pressure than on the local vascular control. If the area affected be a small one, no great change in the general blood pressure is produced by a constriction or relaxation of its arterioles. If, however, the area be large, changes in its vascular resistance cause an appreciable alteration of the arterial pressure. This is particularly true of the great vessels of the splanchnic region, which exercise a preponderating influence upon the vascular control of arterial pressure.

An increased blood flow to one part of the body may be associated with a diminished flow to another part. Dilatation of the splanchnic vessels is usually accompanied by constriction of the surface vessels of the body, and vice versa (Dastre-Morat law). Whether the changes in distant parts of the body are due to nervous reflexes or whether they are more passive in character is not definitely settled.

Although the arterioles may regain a certain amount of tone after all nerves leading to the part have been divided, nevertheless their size in the intact animal is governed mainly by nervous impulses. These impulses are of two kinds: vasoconstrictor and vasodilator. The main vasoconstrictor center lies in the medulla oblongata in the neighborhood of the nucleus of the seventh cranial nerve. It may be stimulated by chemical

changes in the blood or by nervous impulses coming from various parts of the body. Such pressor influences act chiefly by causing a constriction of the splanchnic vessels. Depressor influences either of a chemical or nervous character may also act upon the vasomotor center. The most important of the nervous depressor reflexes arise from the first part of the aorta, and are carried to the medulla by the depressor nerve. Since this nerve is stimulated when the blood pressure is increased, the depressor reflex tends to prevent sudden changes of arterial pressure.

Capillary Pressure.—The walls of the capillaries are usually subjected to considerably less than the arterial pressure, because the main fall in pressure usually occurs in the finer terminations of the arteries. The thin capillary walls suffice to withstand this pressure owing to the small caliber of these vessels, for it is a physical law that, at a given internal pressure, the linear tension on the walls of a tube is proportional to its diameter. Any dilatation of the arterioles subjects the corresponding capillaries to a greater internal pressure and increases their size. To what extent and under exactly what conditions the capillaries also vary their size in response to physical, chemical or nervous influences has not been determined. It is probable, however, that they possess some independent contractile powers. Thus exposure to cold often heightens the color of the skin, even though the blood flow through the arm is markedly lessened, the deep cyanosis after exposure being due to this cause. Apparently the cold causes a dilatation of the skin capillaries, not through any increase in the capillary pressure, but through a relaxation of their walls. That such capillary dilatations or constrictions may be of importance in governing the circulation is obvious; yet at the present time we know very little about them.

Blood Flow in Veins.—The flow of blood through the veins depends in part upon the fall of pressure from the small veins to the right auricle. In part it depends upon the fact that certain veins possess valves. The intermittent compression of such veins by movements and by muscular contractions force blood toward the heart. This mechanism is particularly important in the legs, for the venous pressure in the feet is normally only a trifle higher than the venous pressure in the hands. When an individual walks, the venous flow from the legs to the abdominal cavity is maintained not so much by a continuous high pressure in the capillaries and venules of the legs as by the action of the muscular movements on the veins containing valves.

That the superficial veins of the arms possess contractile powers is evident from their large size when the individual is warm and their small size when the individual is chilly, these differences being maintained even though the venous pressure be raised by compressing the upper arm. The size of the portal vein is influenced by nervous impulses that travel in the splanchnic nerves. It is evident, therefore, that the veins are not mere

passive channels for the return of blood, but that they play a more or less active part in furthering and controlling the circulation. A widespread venous dilatation allows blood to collect in these vessels and slows the entire circulation by lessening the blood supply to the right heart. The patient is "bled" into his own veins.

Transient Arterial Hypertension

We have seen that an increase in the arterial blood pressure may be caused by an increased output from the heart, by a general constriction of the arterioles, or by a combination of the two. The transient hypertension associated with muscular exertion is due in the main to an increased output from the heart. The blood flow through the exercised muscles is very markedly accelerated, and the flow through distant portions of the body surface is also increased. We do not know whether the blood flow in the internal organs is increased or not.

Increased Arterial Resistance.—In most other forms of transient arterial hypertension the rise of blood pressure seems to be due primarily to an increase in the arterial resistance. In acute asphyxia, for example, the rise of blood pressure is due to stimulation of the vasomotor center by the venous character of the blood. Either an excess of carbon dioxid or a deficiency in oxygen will cause such a rise of pressure. The immediate stimulus for the vasomotor, as for the respiratory center (page 349), appears to be an increase in acidity, whether this be due to a collection of carbonic acid or of acid products that arise from an insufficient oxygen supply. Rises of blood pressure from acute asphyxia have been observed in man by Külbs. The normal or somewhat increased blood pressure frequently observed during cardiac decompensation (page 47) is due to vascular constriction, and is probably caused by asphyxial changes in the vasomotor center induced by the slow blood flow.

A marked rise of arterial blood pressure accompanies acute cerebral compression. The latter causes an anemia of the vasomotor center with a local lack of oxygen and a local accumulation of carbon dioxid and other acid products. If the anemia is prolonged, however, the lack of oxygen will reduce the irritability of the center, so that it no longer responds to normal or abnormal stimuli.

We have seen that in certain patients suffering from angina pectoris the attacks of pain are regularly associated with a rise of systemic blood pressure. That the pain of angina, in common with other nervous or psychic disturbances, may itself cause a rise of arterial pressure is certain, and this is doubtlessly one cause of the rise during the paroxysms. It is possible also that a general vasoconstriction merely accompanies a constriction of the coronary vessels, and that the latter is the real cause of the

paroxysm, while the former plays simply an accessory part. Finally, in certain forms of the disease, the rise of pressure produced by a general vascular spasm is believed to be the immediate cause of the attacks of pain. This is known as the vasomotor form of angina pectoris.

Acute rises of blood pressure may also occur in paroxysmal dyspnea, in paroxysmal pulmonary edema, in lead colic and in tabetic crises. Whether these rises are direct causes of the paroxysms or whether they result from the pain or from an imperfect aëration of the vasomotor center is, however, uncertain. Pal has brought together a great number of such conditions, and has given to them the common name of "vascular crises."

In Acute Renal Disease.—Special interest is attached to the rises of blood pressure which often accompany acute renal disease, uremia and eclampsia. A moderate hypertension is common in the acute nephritis that follows scarlet fever and in the so-called idiopathic form of acute nephritis. It is rare in the acute nephritides that complicate typhoid fever and diphtheria. Involvement of the renal glomeruli appears to be particularly marked in the forms of acute nephritis that cause an elevation of blood pressure, while involvement of the tubules is more marked in the forms that cause no such elevation. In acute sublimate poisoning, the severe degeneration of the renal tubules is accompanied by a normal or elevated blood pressure.

Hypertension is almost constant in uremia and the blood pressure may rise during the attack and subside after recovery. In anuria also a moderate rise of blood pressure is the rule. In a case reported by Pässler, the blood pressure was 150 mm. Hg. on the sixth day of the anuria, and it rose to 180 on the tenth and twelfth days shortly before death. Brasch observed a remarkable case in which periods of anuria alternated with periods of free urination. During anuria the pressure rose to 180 or 195, while it fell during the periods of urination to 130 or 140 (Fig. 49). Two rises of this type were observed, but in the third and terminal period of anuria little rise of pressure occurred. Apparently, on this occasion, the body failed to react to the stimulus. In prolonged chronic uremia a similar fall of blood pressure may ocur. Fr. Müller has expressed the opinion that the same toxic substances that produce uremia may, in lessened concentration, affect the vasomotor center, thus causing a heightened blood pressure. So far as the incoagulable nitrogen of the blood is concerned, however, it has been shown by Folin and his coworkers that, although patients with chronic hypertension have, in general, a somewhat increased amount of incoagulable nitrogen in the blood, nevertheless the height of the arterial pressure bears no constant relation to the amount of incoagulable nitrogen, and when the latter is reduced by diet no fall of blood pressure necessarily occurs.

In eclampsia there is usually a rise of blood pressure, and in favorable cases the pressure returns to the normal level after delivery.

The hypertension of acute nephritis, eclampsia and uremia is probably not due to anatomical changes in the heart or blood vessels. The rise in pressure may be quite rapid, and has been observed within forty-eight hours after the onset of an acute nephritis. This, together with the subsidence of the high pressure as the disease improves, indicates that the elevated pressure is due to changes in function rather than in structure.

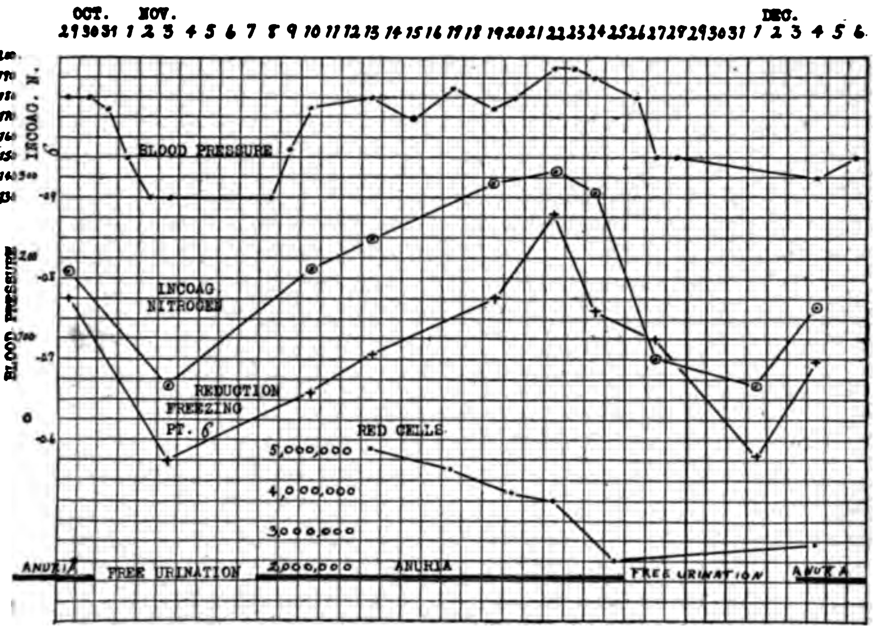


Fig. 49.—The Effect of Intermittent Anuria Due to Malignant Disease upon the Blood and Blood Pressure. Anuria Began about Oct. 22 and Lasted through Oct. 30. This was Followed by Free Urination and by Two Subsequent Periods of Anuria, in the Last of which the Patient Died. During the First and Second Periods of Anuria the Blood Pressure Rose as High as 180 to 195. During the Last Period It Did Not Rise. (Figure Has Been Constructed from a Case Report by Brasch, Deutsch. Arch. f. klin. Med.)

Although direct evidence is lacking, it seems probable that the acute hypertension in such cases is due to a general constriction of the systemic arterioles. Whether this constriction is caused by nervous reflexes from the diseased kidney, or whether, as seems more probable, it is due to toxic substances, is not known.

Chronic Arterial Hypertension

Instrumental methods of determining the blood pressure in man have shown that one of the most important, as well as one of the most common,

pathological disturbances after the age of forty is a continued increase in the arterial blood pressure. The pathogenesis of chronic arterial hypertension is still obscure, as is also its precise relation to the associated renal and arterial diseases. Yet, from the functional standpoint. chronic arterial hypertension constitutes a fairly well defined entity.

Relation to Renal Disease

Richard Bright noted that certain patients dying of kidney disease showed at autopsy an hypertrophy of the heart, and he pointed out that this might be due to the increased arterial tension observed in these patients. From that day to the present the relation between renal disease and arterial hypertension has been a subject of frequent discussion. We have seen that in certain types of acute nephritis an arterial hypertension may appear early, and that it may disappear when the nephritis subsides. Chronic disease of the kidney may or may not be accompanied by an increase in the arterial blood pressure. In amyloid disease of the kidney the blood pressure is rarely increased; in chronic glomerular nephritis it is increased in a moderate proportion of the cases, while in chronic interstitial nephritis hypertension is the rule.

On the other hand, chronic arterial hypertension may exist with no evidence of renal disease. Clinicians not infrequently encounter patients with chronic arterial hypertension who show no changes in the urine. For example, of the 458 patients with systolic pressure of 160 mm. Hg. or over observed by Janeway, 116 showed neither albumin nor casts when the urine was examined, and 91 others showed either albumin without casts or casts without albumin. Although repeated examinations of the urine would doubtlessly have diminished the number of negative urinary findings, nevertheless the fact remains that chronic arterial hypertension is accompanied not infrequently by a normal urine, and this is all the more striking when we remember that individuals over forty may show casts or traces of albumin even when they appear to be normal in other respects, and that the cardiac insufficiency frequently present in patients with hypertension may in itself lead to urinary changes. To such statistics the objection has been raised that renal disease may be present even though the urine is normal. Recent studies by pathological anatomists, however, prove that in certain cases the kidneys of patients with arterial hypertension are normal, and that even though anatomical changes are found these bear no definite relationship to the degree of arterial hypertension.

It has, therefore, been demonstrated that while renal disease and arterial hypertension are frequently associated, the kidney changes cannot be regarded as the sole direct cause of the heightened blood pressure.

Immediate Cause of Chronic Hypertension

Whatever may prove to be the ultimate cause of arterial hypertension, its immediate cause must be either an increased output from the heart or an increased resistance to the escape of blood from the larger arteries. The methods for determining the output from the heart in man are still of uncertain accuracy, but Plesch found no increased output in the cases of hypertension which he examined. Furthermore, the blood flow through the arm is not regularly or materially increased in patients with chronic arterial hypertension, indicating that in this vascular area, at least, the heightened blood pressure causes no increase in the flow of blood. If the heightened pressure were due to an increased output from the heart, both ventricles would do an increased amount of work, and one would, therefore, expect an hypertrophy of both. Pässler has found, however, that in the earlier stages of hypertension the left ventricle alone is hypertrophied, which indicates that the pressure was raised in the systemic but not in the pulmonary circuit. Only in the later stages of the disease, when there had developed a weakness of the left ventricle or an insufficiency of its valves, was the right ventricle affected. Electrocardiographic records also indicate that there is a predominant hypertrophy of the left ventricle in arterial hypertension. It seems fairly certain, therefore, that in the earlier stages of chronic arterial hypertension the left ventricle alone is hypertrophied. This indicates that the cause of the hypertension is neither an increased output from the heart nor an increased viscosity of the blood, for both of these possible causes would affect the left and the right ventricles equally. The immediate cause of the hypertension is, therefore, to be sought in an increased resistance to the escape of blood from the arterial tree of the systemic circuit.

Arterial Changes

Sclerosis of the larger arteries is not necessarily associated with an increased arterial pressure. Studies by different observers have shown that normal or subnormal blood pressures exist in at least 27 per cent of all patients with clinical arteriosclerosis, and pathologists have been equally unsuccessful in correlating cardiac hypertrophy and arteriosclerosis. Ophüls, for example, found that cardiac hypertrophy was absent in 35 per cent of all subjects with marked arteriosclerosis, and that in only about half of these could any general cause, such as malnutrition, be held accountable for the lack of hypertrophy. The earlier work of Hasenfeld and of Hirsch seemed to indicate that sclerosis of the larger arteries produces cardiac hypertrophy only when the splanchnic vessels or the aorta above these was diseased, but Longcope and McClintock demonstrated that obstruction of this important area does not necessarily lead to hyper-

tension or to cardiac hypertrophy. It seems certain, therefore, that sclerosis of the larger arteries is not an immediate cause of arterial hypertension. Nor should one expect it to be so, for we know that the main resistance to the onward flow of blood is encountered not in these vessels, but in the terminal arterioles and capillaries.

Arteriolar Obstruction to Blood Flow.—More and more the opinion has gained ground that chronic arterial hypertension is due to an obstruction to the flow of blood through the smaller arterioles throughout the body. Hypertension is frequently, though apparently not invariably, accompanied by a general sclerosis of the smaller arterioles, a view long since advocated by Gull and Sutton. It is not to be assumed, however, that such a sclerosis causes hypertension by a permanent and immobile reduction in the arteriolar lumina, for it is inconceivable that the vessels generally should become so immobile as to permit none of those extensive variations in local blood flow, which are necessary for the proper functioning of the different organs of the body. The reductions of pressure produced in some patients by the administration of the nitrites indicate that some of the vessels, at least, are capable of dilatation, while the transient rises of blood pressure, to which these patients are peculiarly liable, indicate that their vessels show an unusual tendency to vascular spasm. We believe, therefore, that chronic arterial hypertension is not due to an anatomical narrowing alone, but to a narrowing that is in part caused by an increased tone of the muscle fibers surrounding the arterioles.

In a small number of cases of chronic arterial hypertension, no definite anatomical changes have been found either in the kidneys or in the arterioles. The hypertension, in such cases, would seem to be due to an increase in the tone of the arterioles throughout the body which is purely functional in character. Indeed certain clinicians as well as certain pathologists have held that the functional changes in the arterioles may antedate the sclerotic changes, and that the increase in arteriolar tone either plays a primary rôle in producing vascular disease, or that both are due to a common cause.

It seems probable, therefore, that the immediate cause of chronic hypertension is always a narrowing of the arterioles. In some cases, and perhaps not infrequently in the earlier stages of the disease, hypertension is associated with no demonstrable anatomical disease. The sclerotic changes, often found at autopsy in the smaller arteries, tend to narrow these vessels mechanically, but in addition they may cause a tendency to increased arterial tone and spasm. That sclerosis of the larger arteries should frequently be associated with changes in the terminal arterioles is evident, but the relation is not an invariable one. Sclerosis of the larger vessels, therefore, does not necessarily cause a high blood pressure. The renal changes of chronic interstitial nephritis are now attributed by many pathologists to sclerosis of the smaller renal vessels. Such sclerosis is usu-

ally associated with sclerotic changes elsewhere, and the renal changes are, therefore, regarded as a local manifestation of a general arteriolar disease. It is certain, however, that disease of the kidney in itself is capable of increasing the blood pressure. The hypertension associated with transient anuria and acute nephritis, as well as that which follows an excision of the major portion of the renal substances, can be explained only in this way.

Secondary Lesions

The symptoms and accidents associated with hypertension depend in part upon the hypertension itself, in part upon the associated sclerosis of the blood vessels in particular organs. Practically every patient suffering from chronic hypertension has an *hypertrophy of the heart.* In its earlier stages at least, this hypertrophy affects mainly or solely the left ventricle. If the left ventricle weakens, however, there develops a pulmonary stasis with hypertrophy and dilatation of the left auricle and hypertrophy of the right ventricle. Eventually the right ventricle may also weaken and become dilated. These changes in the heart are due, in part, to the extra work thrown upon the left ventricle by the increased pressure in the aorta. In part they are due to nutritional disturbances of the myocardium, owing to sclerosis of the coronary arteries.

Cardiac irregularities are rather common in patients suffering from chronic arterial hypertension. The most frequent of these are ventricular extrasystoles, which are caused partly by the increased pressure itself and partly by myocardial changes. A weakness of the left ventricle relative to the high pressure in the aorta occasionally causes a pulsus alternans. Finally, in the stage of decompensation auricular fibrillation is common.

Anginal pains occur with unusual frequency in patients with chronic arterial hypertension. These are due in part to the myocardial or coronary disease, and in part probably to a vascular spasm, either of the coronary vessels or of the arterioles throughout the body.

When sclerosis of the arterioles affects the vessels within the cranial cavity, the patients are apt to show mental deterioration, transient paralyses, losses of memory, or serious apoplectic *insults.* The more serious of these *cerebral changes* are due to hemorrhages or thromboses. In addition there may be an abnormal tendency to vascular spasm to which has been attributed some of the more transient of the cerebral seizures.

When disease of the arterioles affects particularly the renal vessels, the signs and symptoms of a *chronic interstitial nephritis* result. In a certain number of patients, renal insufficiency with a terminal uremia dominates the clinical picture.

Certain patients with chronic arterial hypertension show unusual fluctuations of blood pressure, which appear to be due to an abnormally

labile set of arterioles that contract excessively in response to various stimuli. Such sudden rises of blood pressure probably play a part in precipitating certain attacks of angina pectoris or in causing paroxysms of pulmonary edema. In addition to such *general vascular crises,* patients with chronic hypertension appear liable also to *local vascular spasms.* Such local spasms in the coronary arteries may be responsible for certain attacks of angina pectoris. Local spasms in the cerebral arteries may be responsible for certain of the transient cerebral attacks to which these patients are particularly subject. Local spasms in the arteries of the legs have been held responsible for certain types of intermittent claudication. Our exact knowledge concerning such local vascular spasms is, however, rather fragmentary.

Hypotension

Hypotension may be due either to a diminished output from the heart or to an unusually rapid escape of blood through the arterioles, or to a combination of the two factors. The diminished output from the heart may be due to a primary cardiac weakness, although, as we have seen, the failing circulation in heart disease is often associated with a normal or even with an increased blood pressure, owing to a compensatory constriction of the peripheral arterioles. The diminished output from the heart may also result from a lessened supply of blood to the heart. This may be due to a diminished amount of blood in the vessels from hemorrhage, or it may be due to a collection of blood in the veins or capillaries owing to a loss of tone in these vessels. Here again, however, there seems to be a tendency on the part of the arterioles to compensate for a diminished cardiac output by increased constriction.

Chronic hypotension has been observed in various wasting and febrile diseases. Among the latter, typhoid fever and active tuberculosis appear particularly liable to produce low blood pressures. In Addison's disease the blood pressure is frequently but not invariably lowered.

Syncope

Syncope is caused by an anemia of the brain, which usually results from a sudden reduction of the arterial blood pressure. The cause of this abrupt fall may lie either in the heart or in the blood vessels. The occurrence of syncopal attacks in patients who have a slow pulse was noted by earlier pathologists (Morgagni) and clinicians, and this symptom complex has been called the Stokes-Adams syndrome. Although the slow pulse in such cases is usually due to an interruption in the passage of impulses from the auricles to the ventricles (heart block), it may be due to other causes. In a patient whose history is reported by Laslett, for example,

the syncopal attacks were associated with intermissions of the entire heart's action that lasted from four to eight seconds. Or, again, the slow pulse and the faintness are due to a succession of ineffective ventricular extrasystoles which expel little or no blood into the aorta. Ventricular fibrillation, which is closely related to such a succession of extrasystoles, is a possible cause of fatal cardiac syncope. Fainting attacks may also be associated with extreme tachycardia. An excessively rapid heart rate diminishes the total ventricular output, and especially is this so when the auricles and ventricles contract simultaneously.

Vascular Relaxation and Cardiac Inhibition.—The common type of syncope, that which occurs during emotion, is usually attributed to vasomotor influence, and particularly to a relaxation of the terminal arterioles in the splanchnic area. Dr. Agnew, while a member of my staff, had the opportunity of listening to the heart action of two normal students during the syncope that occurred while they were undergoing a routine medical examination. In both cases the syncope was accompanied by a very marked slowing or temporary cessation of the heart sounds. It is probable, therefore, that the emotional type of syncope is, in some cases at least, caused by cardiac inhibition rather than by a vascular relaxation.

An interesting form of syncope is that which occasionally occurs when a patient passes suddenly from the recumbent to the upright position. In this case the large vessels of the abdomen dilate temporarily under the increased pressure to which they are subjected. The venous flow to the heart is lessened, and the arterial pressure is not maintained at a sufficiently high level to supply the brain with blood.

Effects of Hemorrhage

It would seem that a loss of blood would always cause a considerable lowering of the arterial pressure, because the imperfectly filled blood vessels would send less blood to the heart. As a matter of fact, although the blood pressure always tends to fall during considerable hemorrhages, the fall is rarely as marked as one might anticipate. A variety of physiological factors tend to counteract the fall of pressure during moderate hemorrhages. The augmented breathing hastens the venous flow from the abdomen, the accelerated heart rate tends to increase the total cardiac output per minute, and there is a constriction of the peripheral vessels which assists in maintaining the blood pressure. To these may be added the fact that the fluid lost by the hemorrhage is often replaced with extraordinary rapidity from the tissue fluids (page 586). By reason of these compensatory factors small hemorrhages may produce no fall of arterial pressure, while the fall in larger hemorrhages is often surprisingly little. In very large and rapid hemorrhages, of course, the pressure falls and syncope supervenes.

Surgical and Traumatic Shock

It is well known that patients who have been severely injured may pass into a peculiar condition to which the name of traumatic shock has been given. Meltzer describes the symptoms and signs of shock as follows: "A state of general apathy, reduced sensibility, extreme motor weakness, great pallor, rapid small pulse, thready soft arteries, irregular gasping respirations and subnormal temperature." The circulatory manifestations are usually a prominent feature of the condition. The blood pressure at first may be normal but ultimately in severe cases it falls, and at the time of death has reached a very low level. A similar group of symptoms may occur during or after surgical operations and is spoken of as surgical shock. Although deep anesthesia and severe hemorrhage predispose to surgical shock they are not believed to be its sole cause.

Pathogenesis.—Crile has maintained that surgical as well as traumatic shock is caused by an exhaustion of the vasomotor center. The abnormal sensory impulses arising from the injured parts of the body are carried to the central nervous system, and stimulate the vasomotor center in the medulla. At first these stimuli raise the blood pressure, but eventually, according to Crile, they cause an exhaustion of this center with a consequent lowering of the blood pressure. W. T. Porter and other investigators have demonstrated, however, that long-continued stimulation of the nerve trunks leading to the extremities almost invariably fails to cause either the symptoms of shock or a marked depression of the blood pressure, provided care be taken to avoid hemorrhage and excessive etherization. On the other hand, experimental shock may be produced quite regularly by opening the abdominal cavity and handling or even exposing the intestines and other abdominal viscera.

Henderson found that he could produce shock by overventilating the lungs, and he believes that shock results from a removal of carbon dioxid from the blood and tissues (acapnea) as a result of excessive respiration. The shock that follows exposure of the intestines is, according to Henderson, due to losses of CO_2 from the exposed viscera. The latter explanation has been disproved, however, by those who have been able to produce shock by handling the intestines while carbon dioxid losses were prevented. Furthermore, according to H. H. Janeway, the shock produced by excessive pulmonary ventilation is caused by a mechanical interference with the return of blood from the abdominal organs to the heart. Janeway and Jackson have shown that a mechancial obstruction of the inferior vena cava for a limited period of time may be followed by the classical signs of shock.

That there is no exhaustion of the vasomotor center in shock has been proved by Porter who found that the rise of pressure produced by stimulation of a peripheral nerve may be as great in the shocked animal as in the normal. Mann also showed that asphyxia causes the same rise of pres-

sure in shocked as in normal animals. The pallor of the skin which occurs in shock may be due either to an active constriction of the peripheral blood vessels or to a passive draining of the blood into the internal organs. That certain peripheral vessels may preserve their tone during shock has been demonstrated by various observers. For example, Seelig and Joseph cut the vasomotor nerves leading to one ear of a white rabbit and thus caused a local paralytic dilatation of the vessels in this ear. After intense shock had been produced in the animal the abdominal aorta was clamped just below the diaphragm, so as to raise the arterial pressure in the anterior portion of the body. Under such circumstances the denervated rabbit's ear became engorged with blood while the normal ear usually remained very pale. Even in intense shock, therefore, the vessels in the rabbit's ear maintain their tone.

Henderson has shown, furthermore, that in the preliminary stages of shock there is an increase rather than a diminution in the total resistance to the escape of blood from the larger arteries. On recording the volume of blood expelled by the ventricles, he found that the first indication of oncoming shock is a slow diastolic filling of the ventricles, due apparently to a low venous pressure. Gradually, the diastolic filling of the ventricles as well as their systolic output became diminished. Not until the arterial blood stream had been reduced to about one-third the normal was there a marked and rather rapid fall of the arterial pressure. According to Henderson's observations, therefore, the earlier stages of shock are characterized by a diminished cardiac output and the blood pressure is maintained at this time by a compensatory constriction of the peripheral arterioles. Henderson believes that the diminished output from the heart is due to stasis of blood in the veins, and that the essential change in shock is an abolition of venous tone. Experiments by other investigators have tended to confirm these conclusions. Thus H. H. Janeway has been able to produce shock by mechanically obstructing the inferior vena cava for a limited length of time and afterwards releasing the obstruction. Such an obstruction apparently caused a loss of tone in the veins and capillaries of the abdominal viscera. Furthermore, Morrison and Hooker have found: (1) that in shock the pressure fell in both the systemic and portal veins; (2) that the weight of an isolated loop of intestines increased; and (3) that perfused fluids flow less rapidly through the organs of shocked animals.

Theory of Surgical Shock.—The cardiovascular changes during surgical shock appear to be as follows: Owing to various causes and particularly to exposure and handling of the intestines, the blood accumulates in the veins and the capillaries of the abdominal viscera by reason of a loss of venous and capillary tone. The withdrawal of this blood from the circulation leads to a diminished venous pressure and to a diminished filling and output from the heart. At first there is no fall of blood pressure, for the lessened cardiac output is neutralized by an increased

constriction of the peripheral arterioles of the body. Ultimately, however, this compensatory mechanism fails and the hypotension of advanced surgical shock results.

Circulatory Failure in the Infectious Diseases

It is well known to clinicians that the circulation is altered during the infectious diseases and that patients not infrequently die with manifestations of circulatory failure. Even in the earlier stages of infection the pulse becomes more rapid and the pulse form changes. As failure approaches the pulse becomes smaller and may almost disappear, the skin becomes cool and either pale or cyanotic, the body temperature may fall, and the patient is greatly prostrated. Such are the symptoms of the circulatory collapse during infections. Clinicians have long recognized that these symptoms resemble those of surgical shock rather than those of cardiac insufficiency. There is, as a rule, no edema, no enlargement of the heart and no rise of venous pressure. Dyspnea is not an early symptom. The arterial blood pressure may fall early or it may be maintained almost to the last. Only at the end is there a marked fall.

That the heart itself is often injured by infectious processes cannot be denied. In acute rheumatic fever definite changes in the myocardium have been demonstrated, diphtheria toxin injures the heart muscle, and changes in the heart muscle have been found in other infections. Yet cardiac insufficiency seems to play a minor part in most cases of circulatory failure during infections. This is evident not only from the absence of the usual clinical signs of cardiac insufficiency, but also from experimental studies, which have shown that at the time of circulatory failure the heart may still be able to cause a marked rise in the blood pressure when the abdominal aorta is clamped.

Pathogenesis.—According to the experimental work of Romberg, Pässler, Heineke, and their coworkers, the failure of the circulation during the infectious diseases is due, in the main, to a paralysis of the vasomotors in consequence of damage to the vasomotor center in the medulla oblongata. The recent work of Porter and his associates, however, has demonstrated that the vasomotor reflexes in experimental pneumonia and experimental diphtheria are normal, and Newburgh and Minot have shown that the blood pressure is not unusually low in fatal cases of pneumonia. It would appear, therefore, that the vasomotor apparatus may maintain its integrity even in severe and fatal infections.

That the circulation is frequently altered in the infectious diseases, however, seems certain, for the author has found that the form of the volume pulse in the arm usually changes in a characteristic manner (Fig. 53), and that, in the more severe types of infections, the size of the volume pulse in the arm lessens. Although the explanation of these changes

in pulse form is still uncertain, it may be pointed out that they may be brought into accord with the hypothesis already advanced for surgical shock; viz., that there is a collection of blood in the abdominal veins or capillaries, and that as a result of this collection there is an insufficient supply of blood to the heart. The resulting diminution in the cardiac output might cause the characteristic fever pulse even though the blood pressure were maintained. The loss of venous tone also explains the normal or reduced venous pressure observed by Tabora during infections. Finally, the abdominal organs are often found at autopsy to be filled with blood and in experimental infections the capillaries may show pathological changes. The unusually rapid onset of circulatory collapse in acute general peritonitis is due to the effect of the local inflammation upon the abdominal vessels. From analogy with surgical shock, as well as from various clinical and anatomical data, therefore, the hypothesis is advanced that the cause of the circulatory collapse in severe infections is a stagnation of blood in the abdominal veins and capillaries. The vasomotor apparatus which governs the resistance in the peripheral arterioles may still be active, and, in spite of a reduction in the cardiac output, the blood pressure may be maintained at a normal or nearly normal level until shortly before death.

The Pulse Pressure

During each pulse beat there is a fluctuation of pressure within the arteries. The highest pressure attained is called the *maximum pressure,* the lowest is called the *minimum pressure,* while the pressure recorded by an instrument that dampens the fluctuations is called the *mean pressure.* As a rule all these pressures vary in the same direction, but the variations in the maximum pressure are usually the greatest, while the variations in the minimum pressure are usually the smallest. In speaking of high or low pressure, therefore, we usually assume that all three pressures are raised or lowered, as the case may be.

Increased and Diminished Pulse Pressure.—The difference between the maximum and the minimum pressures, the so-called *pulse pressure,* represents the variation in pressure with each heart cycle. It is caused by the expulsion of blood from the left ventricle into the elastic arterial tree. The pulse pressure will be greater: (1) when the systolic output from the heart is increased or when it is expelled very suddenly; (2) when the main arteries have a small volume; and (3) when the main arteries are rigid. Conversely the pulse pressure will be diminished when the systolic output is small or the main arteries are elastic and of large size.

The part played by these various factors in an individual case are, however, difficult to determine. During exercise the pulse pressure is increased, and this is probably due mainly to an increased output at each

beat of the heart. In sclerosis of the large arteries the increased rigidity of the arterial walls tends to increase the pulse pressure. Strassburger has shown, however, that this rigidity is often compensated for to a greater or lesser extent by an increase in the lumina of the vessels. As a matter of fact, the pulse pressure is often moderately increased in general arteriosclerosis, but this is rarely very marked and is often absent.

Effect of Aortic Insufficiency.—One of the most characteristic effects of an aortic insufficiency is the increased pulse pressure. The escape of blood back into the ventricle during diastole causes a very unusual lowering of the diastolic pressure. The increased ventricular output at the next systole causes the marked fluctuation in pressure that characterizes this lesion. According to Wiggers, the large pulse pressure is due in part to the suddenness of the ventricular output.

Local Vascular Changes

While the vascular resistance as a whole exercises a dominant influence on the systemic blood pressure, variations in local resistance determine to a large extent the circulation through each individual organ. Only in the case of the brain are such variations of minor importance. Elsewhere the local flow is governed mainly by the local arteries. Other things being equal, a relaxation of the local arterioles causes a more rapid flow of blood through the vascular area that they supply, a rise of pressure in the local capillaries and an increase in the capillary lumina. Such changes characterize an *active hyperemia*. If the venous outflow from an organ be obstructed, the pressure in and the size of the veins and capillaries are also increased. The local blood flow, however, tends to be diminished. This is called a *passive hyperemia.*

Conversely, *local anemia* of an organ may be due (1) to an increased venous outflow, as when the hand is held above the head; or (2) it may be due to a diminution of the arterial inflow, owing to an obstruction or a constriction of the arteries that lead to the part.

Loss of Capillary Tone.—In the conditions just described the mechanical relations are obvious. They are less evident, however, in those cases where a reduction of the arterial flow to an organ is followed by a dilatation of its capillaries. It is well known, for example, that the occlusion of an artery leading to the lungs or to the intestines does not usually cause an anemia of the part involved with the formation of an anemic infarct, but that, on the contrary, it leads to a marked collection of blood in the capillaries of the affected area, thus producing the so-called hemorrhagic infarct. This extra blood may enter the capillaries either from anastomosing arteries or capillaries or by a back flow from the veins. Since no obstruction exists to the escape of blood through the veins, the

collection of blood in the infarcted area can only be due to a relaxed condition of the local capillary walls. This loss of capillary tone probably depends in part upon nutritional disturbances produced by the slow flow of blood through the region, in part it depends upon the loose structure of the tissues involved.

Effect of Cold.—The intense cyanotic color of the skin that often accompanies prolonged exposure to cold appears to depend upon similar vascular changes. Exposure of the hands to cold usually produces at first a pallor of the skin, which is evidently due to a constriction of the cutaneous arterioles. When the exposure is prolonged, however, the color is heightened, and it usually becomes more or less cyanotic. That the blood flow through the skin is diminished is evident both from the cyanosis and from determinations of the rates of flow. Almost universally, therefore, cold produces a constriction of the cutaneous arterioles and a slow flow of blood through the skin. The variations in color are caused by the varying amounts of blood that collect in the skin capillaries. The dilatation of these capillaries when the arterioles are constricted is caused either by a lessened capillary tone, or possibly by a constriction of the corresponding veins which interferes with the escape of blood.

The arteries or veins to a part may be narrowed mechanically by emboli, thrombi, changes in their walls, or external pressure. When such mechanical obstructions exist the pathogenesis of the local circulatory changes is evident.

Effect of Inflammation.—During inflammation the local blood flow is, at first, increased and there is an active hyperemia. Later, however, certain capillaries may show a slow blood current under the microscope. This slowing may depend upon various factors, among which are a collection of cells along the walls of the capillaries and compression of the vessels by the products of inflammation. The total blood flow through an acutely inflamed area is, however, almost invariably increased. This is rendered probable by the fact that the skin overlying acute inflammatory processes near the surface of the body is always warmer to the touch than the surrounding surface. Furthermore, direct as well as indirect measurements of the rate of blood flow through an inflamed extremity have usually shown that this is greater than in the corresponding sound extremity.

Other Vascular Changes.—Pathological alterations in the blood flow through various regions of the body may be due to functional changes in the tone of the local arteries. For example, in some individuals an exposure to moderate cold is followed by an active hyperemia of the cutaneous vessels with increased blood flow. In other persons the cutaneous arterioles contract excessively on exposure to cold. Among other abnormal vascular reactions is the marked pallor, hyperemia or local edema that appears in certain (neurotic) persons on mechanical irritation of the skin (dermatographia). Such altered reactions may be purely functional in character

and in no way due to organic disease. It is noteworthy, however, that the tendency to vascular spasm is frequently associated with anatomical disease of the blood vessels, and that, in some cases, it is not easy to differentiate the relative parts played by structural and by functional changes. Of the diseases usually attributed to vascular spasm, the most important is Raynaud's disease. In this disease, arterial anemia, arterial anemia with capillary congestion, or arterial anemia with necrosis may occur. In certain patients with intermittent claudication the change in the circulation of the legs is attributed to a spasm of the local vessels. Spasm of the central artery of the retina has been observed in patients with the transient blindness that occasionally accompanies renal disease. That local vascular spasms may also occur in internal organs seems probable both from analogy with observations on accessible arteries, and from the fact that transient rises in the blood pressure which are due to a general vascular constriction are frequently associated with local symptoms. We have, however, no exact knowledge of such local vascular spasms in the internal organs of the body. Presumably, however, spasm of the cerebral arteries is responsible for certain of the transient cerebral attacks so common in patients with cerebral arteriosclerosis or chronic hypertension. Spasm of the coronary arteries may play a part in the etiology of angina pectoris. Spasm of the renal arteries causes the diminished secretion of urine in acute strychnin poisoning. Still other examples of local vascular spasm are described by Pal in his monograph.

Form of the Arterial Pulse

The arterial pulse is produced by the intermittent expulsion of blood from the left ventricle into the aorta. This produces intermittent movements of the blood along the arteries (displacement pulse) with intermittent variations in the size of the blood vessels (volume pulse) and intermittent fluctuations in the pressure within the arteries (pressure pulse). These pulse changes spread in a wavelike manner over the entire arterial tree. The small size of the terminal arterioles and capillaries retards any sudden movements of the blood in these vessels, and thus tends to convert the intermittent flow that is present in the larger arteries into a continuous pulseless flow.

From the earliest times the pulse has been an object of interest and study. From it one may estimate the rate and rhythm of the heart, the condition of the arterial wall, and, to some extent, the systolic and diastolic blood pressures. The size of the pulse is governed partly by the output from the heart and partly by the size of the different arteries and the elasticity of their walls. When, as in palpating the radial pulse, the artery is compressed with sufficient force to empty it between beats, the

size of the artery plays an important part in governing the amplitude of the palpable pulsations.

Pulse Recorders.—The form of the arterial pulse can be estimated only very imperfectly by palpation. For the accurate study of pulse form instrumental records are necessary. Unfortunately, nearly all of the earlier instruments used in the study of arterial pulse form were subject to grave defects. In order to record the rapid changes that occur during the various phases of the arterial pulse, an instrument must be highly efficient and, in particular, it must itself possess a rapid inherent rate of vibration, in order to follow faithfully the sudden changes in form which characterize the arterial pulse. To Otto Frank belongs the credit for having analyzed the theoretical requirements of pulse recorders, and for having developed a method by means of which such instruments can be made sufficiently rapid to follow accurately the contour of arterial pulse curves. The most essential change introduced by Frank was the replacement of the usual writing level of the recording tambour by an imponderable beam of light. This beam is reflected from a small mirror that is attached to a small-sized tambour and records are obtained by photographing the movements of this beam on a traveling strip of film or photographic paper.

The carotid pulse of the dog, as recorded in this manner, shows the following characteristics (Frank): (a) a slight undulation synchronous with the auricular systole; (b) a brief wave during the presphygmic period of ventricular systole; (c) a sharp rise of pressure with the first expulsion of the blood; (d) a rounded systolic apex which is interrupted by (e) a sharp incisure with after-vibrations due to the closure of the semilunar valves; and (f) a gradual fall of pressure during diastole (Fig. 50). According to Frank, the pressure pulse in the peripheral arteries differs from the central pulse partly because the finer vibrations are lost, and partly because the dicrotic notch becomes more prominent (Fig. 51). Wiggers has shown, however, that under pathological conditions the carotid pulse may show a form in many ways similar to Frank's "peripheral pulse."

Fig. 50.—The Central Carotid Pulse of the Dog. (After Frank, Ztschr. f. Biol.)

Direct pressure records from the arteries in man cannot be obtained by bloodless methods. Nevertheless the application of a receiving tambour over the course of an artery has shown that in man also the pressure pulse has many of the characteristics described by Frank, and that as one proceeds from the center to the periphery, there is a gradual loss of the

finer arterial movements. According to Müller and Weiss, the central details are transmitted more perfectly to the periphery when the arterial walls are in a condition of high tone.

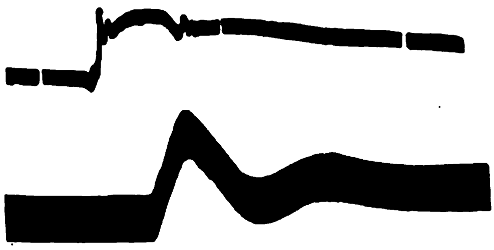


Fig. 51.—The Carotid (Upper) and the Peripheral Arterial Pulse (Lower). (After Frank. Ztschr. f. Biol.)

Sustained and Collapsing Pulse in Arm.—The volume pulse in the arm of man may be recorded by connecting a suitable plethysmograph with a Frank recorder. Furthermore, if the veins leading from the arm are obstructed for a brief interval, the movements of blood in the arm arteries may be accurately recorded. Records of the volume pulse in the arm of man allow us to distinguish two fundamental types of peripheral pulse in man. In the first of these, which we shall call the sustained pulse, the sudden entrance of blood into the arm during early systole is followed by a gradual decline in the tracing (Fig. 52). The uniformity

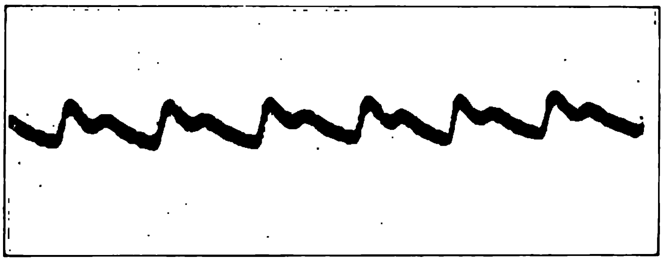


Fig. 52.—Sustained Volume Pulse in the Arm of Man.

of this decline is broken more or less by the dicrotic and smaller secondary waves. The second type of volume pulse, which may be called the poorly sustained, pointed, or collapsing pulse, is characterized by an abrupt diminution in the arm volume immediately after the entrance of the primary pulse wave (Fig. 53). In such a pulse the smaller secondary waves are usually absent, while the dicrotic wave may be exaggerated, nor-

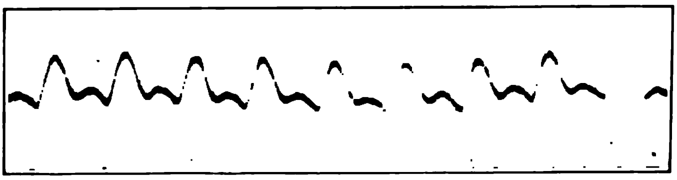


Fig. 53.—Pointed Volume Pulse in the Arm of Man during Fever. Note that the Fall After the Primary Pulse Wave Approaches the Base Line.

mal or absent. When it is unusually marked the pulse is dicrotic. Determinations of the movements of blood in the arm arteries have shown that the abrupt fall in volume, which characterizes the pointed pulse, is associated with a backward movement in the column of blood in the brachial artery, owing to a reflection of the pulse wave in the arm (Fig. 54). Transitions between the two types of peripheral pulse are common.

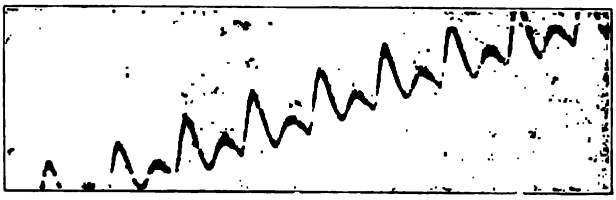


Fig. 54.—Dicrotic Pulse in Fever. The Veins in the Arm Have Been Momentarily Obstructed and a Downward Movement of the Tracing Indicates an Outflow through the Brachial Artery. Note that the Collapse After the Primary Wave Is Due to a Reflection of the Primary Wave Out of the Arm Arteries. (After Hewlett, Arch. Int. Med.)

A pointed type of pulse may be produced quite regularly in young individuals by therapeutic doses of nitroglycerin, and it is always present in the typical collapsing pulse of aortic insufficiency (Fig. 55). In such cases the pointed or collapsing pulse seems to be due to a relaxation of the larger arm arteries without a corresponding relaxation of the terminal arterioles in the arm. The large pulse wave, which enters the arm, is reflected back again by the resistance opposed to its further progress in the finer terminations of the arterial tree in the arm. The pointed type of pulse may also be produced by a small and sudden output from the heart. In auricular fibrillation, for example, the smaller pulse waves may be of a collapsing type, while the larger waves are sustained.

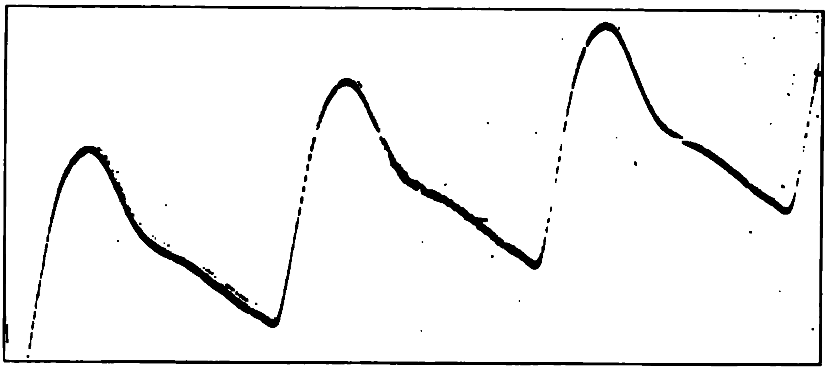


Fig. 55.—Markedly Collapsing Pulse of Aortic Insufficiency. Veins in the Arm Obstructed. Note that the Portion of the Collapse which Precedes the Dicrotic Notch Occurs during Systole and Is Due to the Same Reflection as Fig. 54. The Later Diastolic Fall in the Tracing Is Probably Due to the Leak into the Left Ventricle during Diastole. (After Hewlett and Van Zwaluwenburg, Arch. Int. Med.)

Particular interest is attached to the pointed pulse in the arm for the

reason that this occurs with great frequency during the course of the infectious diseases (Fig. 33). It is in fact the rule among fever patients, and it may persist for some time after the temperature has fallen to normal. With a failing circulation during fever the pointed pulse usually becomes progressively smaller. These changes may occur even though the blood pressure is normal or but slightly diminished, and they indicate that the circulation is usually altered during infections. The exact cause of the pointed febrile pulse is still uncertain, but as we have seen several factors may contribute to its production. Among these are: (1) a relaxation of the larger arteries; and (2) a diminished and sudden output from the heart.

We have pointed out that there is reason to believe that the cardiovascular collapse of the infectious diseases is caused by a loss of tone in the abdominal veins and capillaries which allows blood to collect in these vessels and thus lessens the cardiac output. The collapsing type of pulse observed in febrile collapse is, therefore, probably due to the sudden output of a small amount at each cardiac contraction. Possibly also the collapsing pulse observed in the earlier stages of infections is due to a similar cause, although on this point there is no definite data at the present time.

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Chapter II

Digestion and Absorption

Disturbances in the Esophagus

Physiological Considerations

The pharynx and the esophagus serve to carry the masticated food through the thoracic cavity into the stomach. Their function is purely a mechanical one and they take no part in the chemistry of digestion. The act of deglutition may be divided into three parts: (1) the passage of food from the mouth into the esophagus; (2) its translation through the esophagus; and (3) its entrance into the stomach through the cardiac sphincter.

First Part of Deglutition.—During the first portion of deglutition the mass to be swallowed passes out of the oral cavity into the upper portion of the esophagus. The bolus is gathered on the top of the posterior portion of the tongue, the edges of the tongue are closely applied to the hard palate and the teeth, so as to prevent the escape of food into the mouth, and the food is suddenly forced back into the pharynx and upper esophagus by an upward and backward movement of the tongue. The nasopharynx is closed off by a contraction of the posterior constrictors of the pharynx and by an elevation of the soft palate. The opening into the larynx is closed so as to prevent the entrance of food into the respiratory tract. The exact mechanism of this closure is still somewhat uncertain, although the recent observations of Küpferle seem to confirm the older view that it is accomplished by having the epiglottis close like a lid over the top of the larynx.

Pathological disturbances in this first portion of the act of swallowing are usually due to some failure to close off the openings into the nasopharynx or larynx, so that some of the food escapes either into the nose or into the respiratory passages. Paralyses affecting the upper pharynx and soft palate, such as occur most frequently after diphtheria, permit food and particularly liquids to return through the nose. A failure to close the larynx is far more serious, for in this case the food or liquid enters the respiratory tract. From here it may be removed by the usual

protective mechanisms, particularly coughing. When, however, the sensations and reflexes of the respiratory tract are diminished, either on account of general unconsciousness from acute alcoholism, surgical anesthesia or apoplexy, or on account of a local anesthesia from organic nervous lesions, the dangers attending such a false passage of material into the larynx are materially increased and an aspiration pneumonia may result.

Second Part of Deglutition.—The physiological mechanism of the second portion of swallowing, i. e., the passage of food or liquids through the esophagus, has been the subject of considerable discussion. The older physiologists believed that the passage of food through the esophagus was effected solely by the peristaltic movements of its musculature. The experiments of Kronecker and Meltzer, however, emphasized the fact that liquids may be expelled from the mouth with great velocity and that they may be shot rapidly down the esophagus, reaching the cardiac opening into the stomach ahead of the peristaltic waves. The numerous subsequent studies, which have been made of this second portion of the act of deglutition, have shown that the rapidity with which swallowed material passes through the esophagus varies in different animals, and varies in a given animal with the character of the material swallowed. Solid food usually moves down the esophagus slowly and regularly, being propelled by peristaltic waves. Liquids, on the other hand, pass down much more rapidly. Semisolid materials occupy a position intermediary between the two.

Third Part of Deglutition.—When fluid or semifluid material arrives early at the cardia only a very small part enters the stomach immediately. The greater part is held in the esophagus by the tonic contraction of the cardiac sphincter and is forced into the stomach by peristaltic waves which follow down the esophagus. Successive swallows of fluid tend to lessen the tonus of the cardiac sphincter and, according to Kraus, they also increase the esophageal peristalsis. This may explain the fact that many patients, who experience difficulty in swallowing, attempt to facilitate the passage of food down the esophagus by sipping liquids slowly.

Mechanical Obstruction of the Esophagus

Interference with the passage of swallowed material through the esophagus is usually due to mechanical causes. The most important of these are malignant tumors originating in the esophagus and cicatricial stenoses following ulcerative disease or corrosive poisons. Less commonly the mechanical obstruction is due to compression of the esophagus by masses, such as neoplasms, goiters and aneurisms which lie outside of the tube itself.

Symptoms.—Mechanical obstruction of the esophagus may at first produce no interference with the act of deglutition. Symptoms are usually first noticed during the swallowing of coarse pieces of solid food. The patient may then experience a sensation as if the food stuck at a certain point beneath the sternum. Not infrequently he tries to assist its passage by sipping liquids or by repeated swallowing movements. These attempts, as we have seen, may be of service by increasing the number and force of the peristaltic waves. If the material cannot pass the obstruction, it is sooner or later returned to the mouth. The patient usually distinguishes this regurgitation from true vomiting on account of the absence of nausea and of violent abdominal movements. Regurgitation is not accomplished by antiperistaltic movements of the esophagus, but is effected by an increase of pressure below, combined with a relaxation of the esophagus above.

Dilatation Above Obstruction.—In the earlier stages of a mechanical stenosis the esophageal peristalsis above the obstruction is increased and the muscle layer becomes hypertrophied (Krehl). At first there is little or no dilatation. Gradually, however, the repeated or constant strain on the esophageal wall above the stenosis leads to a more or less marked dilatation of this region. This dilatation may be favored by a weakening of the wall owing to local disease. The dilatation above an obstruction varies greatly in extent and in degree in different patients. When remnants of food remain continuously in the dilated esophagus without being regurgitated back into the mouth, they tend to decompose, and may give a foul odor to the regurgitated material.

Spastic Obstructions

According to Kraus, it is not very uncommon during x-ray examinations to observe transient spasms of the esophagus which cause a brief stoppage of semifluid material. These may cause some regurgitation into the mouth, or the food, after a brief delay, may pass on into the stomach. General esophageal spasms occur in hydrophobia, tetanus and hysterical conditions. They also result from the action of corrosive poisons. After a patient has swallowed carbolic acid, for example, it may be difficult or well nigh impossible to pass a stomach tube. The pain which is occasionally felt beneath the lower sternum, when a large gulp of liquid is hastily swallowed, seems to be due to a spasm of the esophagus or of its cardiac orifice.

Cardiospasm

By far the most important type of functional obstruction of the esophagus is that which is caused by a spasm of the cardiac sphincter, which is located at the entrance of the esophagus into the stomach. This condition of cardiospasm, though relatively rare, is of great practical importance on

account of the excellent results which have followed its treatment by mechanical dilatation of the obstruction. The patient's history is usually a long one. At the onset the swallowing of food may cause sudden spasmodic choking sensations. These are rarely described as actual pain, and are usually referred to the region of the lower sternum. Later there is a regurgitation of the food that has just been swallowed, and still later the food may remain for some time above the cardia, so that regurgitation occurs only at irregular intervals.

In these later stages there is a diffuse dilatation of the esophagus. At autopsy, however, no obstructive cause for the dilatation is apparent. On this account the condition has frequently been described as an idiopathic dilatation of the esophagus. While it is possible that, in some instances, dilatation of the esophagus is a primary and essential lesion, it is certain that, in the great majority of patients, esophageal dilatations without organic obstruction are secondary to, or coördinate with, an excessive tone or spasm of the cardiac sphincter. This view is supported: (1) by the early history of choking sensations which usually precede the regurgitation of food and the esophageal dilatation; (2) by the fact that the peristaltic waves in the esophagus when observed by x-ray may be normal or increased; and (3) by the observation that at autopsy the circular fibers of the esophageal muscle are often found to be hypertrophied. The important rôle played by cardiospasm in such patients is finally established by the brilliant therapeutical results which have followed mechanical dilatation of the cardiac sphincter.

Cause of Spasm.—The cause of the increased tone or spasm of the cardiac sphincter in such patients is not always clear. In occasional cases with typical symptoms there is present some organic disease, such as a carcinoma of the cardiac portion of the stomach. In such cases the spastic cardiac contractions have apparently been produced by an irritation of the local nerves. In the majority of patients, however, no organic cause for the spasm is demonstrable, and signs of a general neurosis may also be absent. The cardiospasm in such cases is due either to some change in the sphincter itself or to some change in its innervation.

Innervation of Esophageal Muscle.—The esophageal muscle is innervated by the vagi nerves. A stimulation of these nerves produces a powerful and general contraction of the esophagus. At the same time the cardiac sphincter is relaxed, though possibly this relaxation is due to the presence of sympathetic fibers in the vagi. When the vagi are cut in animals there is at first a complete paralysis of the esophagus. Cannon has shown, however, that after a time the lower portion of the esophagus, that lined by smooth muscle, recovers its motility. Peristaltic movements in this portion are initiated whenever food enters, the effective stimulus being an increase in the local tension.

Vagus Section and Cardiac Sphincter.—Vagus section also usually

increases the tone of the cardiac sphincter. Even powerful peristaltic waves in the lower esophagus may fail to force food into the stomach, and there may be difficulty in passing a stomach tube through this portion of the esophagus. In Cannon's experience this increased tone of the cardiac sphincter after section of the cat's vagi is usually transient. After a time the obstruction lessens and food is forced through the orifice without great difficulty. In some animals, however, the recovery is less perfect. The passage of the stomach tube remains difficult and the esophagus becomes markedly dilated and more or less continually filled with food.

It is evident, therefore, that vagus section may produce changes in the function of the cardiac sphincter, which are in many ways analogous to those that occur in the cardiospasm observed in man. The antagonism which has been observed experimentally between the cardia and the remainder of the esophagus is also of clinical interest; for it has been noted in patients that the esophageal dilatation associated with cardiospasm is often more marked and more extensive than the dilatation which follows organic obstruction. It seems, indeed, not improbable that clinical cardiospasm may often be associated with some relaxation of the remainder of the esophagus. If this be true, it would support the hypothesis that cardiospasm in man is due to a paralytic condition of the vagus filaments which supply the esophagus. Kraus has described an anatomical lesion of the tenth nerve in one case of cardiospasm, but other similar cases do not seem to have been reported.

Atony of the Esophagus

Although cardiospasm is doubtlessly responsible for the majority of the cases of so-called idiopathic dilatation of the esophagus, the question as to the occurrence of esophageal atony still remains open. Holzknecht and Olbert have described such a condition, which was characterized by a slow or incomplete emptying of the esophagus when mushy material was swallowed. If the amount swallowed was small it was carried slowly down the esophagus, while if large amounts were taken a portion was left along the esophageal wall. These authors interpret their findings as evidence of relaxation and incomplete contractions of the esophagus. Clinically the condition may or may not be accompanied by symptoms. When present, the latter consist of regurgitation, dysphagia, globus, etc., symptoms which suggest an obstruction to the passage of food through the esophagus. Holzknecht and Olbert believe that esophageal atony is frequently associated with atony of other portions of the digestive tract.

Insufficiency of the Cardiac Sphincter

Food that has once entered the stomach is ordinarily prevented from returning into the esophagus by a contraction of the cardiac sphincter. Cannon has shown, however, that in the cat portions of the gastric material

may pass rhythmically from the stomach into the lower esophagus, from which region they are carried back into the stomach again by peristaltic waves. This regurgitation of gastric contents into the lower esophagus occurs most commonly when the stomach contains a considerable amount of fluid material. Furthermore, those rhythmic regurgitations into the lower esophagus are most marked during early gastric digestion. In the later stages they usually cease, because the heightened acidity of the gastric contents increases the tone of the cardiac sphincter.

Regurgitation in Man.—It seems probable that similar regurgitations may occur in man. So long, however, as the material regurgitated does not irritate the lower esophagus and does not reach the mouth, it causes no symptoms. Hertz has shown that the lower esophagus is far more sensitive to certain chemical irritants than is the stomach itself. When strong alcoholic solutions are introduced into the stomach they produce a not uncomfortable feeling of warmth, but when introduced into the lower esophagus they cause marked burning sensations. It seems probable that the sensations of pyrosis, or "heartburn," which are usually referred to the epigastrium or the lower sternum, and which are not infrequently associated with the return of irritating gastric contents into the mouth, are due, in part at least, to the action of gastric contents upon the lower esophagus. Hertz also found that the lower esophagus was normally insensitive to acid. Pyrosis would, therefore, seem to be due either to a change in sensibility of the lower esophagus toward acid or to the action of substances other than acid.

Regurgitation of material from the stomach into the mouth requires not only a passage of the cardiac sphincter, but also a return of the material up through the esophagus. So far as we know, the latter is never due to antiperistaltic waves.

Eructation.—Eructation of gases takes place with comparative ease. When much gas is present in the upper portion of the stomach it keeps the acid away from the cardiac region. This lessens the tonic contraction of the sphincter and so favors the escape of gas.

Aërophagia

The stomach normally contains a certain amount of air which in the erect posture occupies its upper pole directly beneath the diaphragm. During swallowing, more air is carried with the food into the stomach. Even under normal circumstances, as we have seen, some of this may be expelled from the stomach by a relaxation of the cardiac sphincter and further passage up the esophagus. In this manner the stomach automatically relieves itself of an excess of air. This eructation of gas frequently gives a sense of relief, especially if the abdomen is distended or the heart action is embarrassed.

Pathogenesis.—Under pathological conditions, and especially in patients suffering from general neuroses, dyspeptic symptoms or cardiac distress, the belching of gas may recur repeatedly and enormous quantities of gas may be raised within a brief period of time. This gas is atmospheric air. If such patients are carefully observed, it is usually evident that the eructations are preceded by swallowing movements. Further more, if the swallowing of gas be prevented by keeping the mouth open, either voluntarily or by a spool placed between the teeth, the eructations cease. It is obvious, therefore, that severe and prolonged attacks of gaseous eructations are associated with a swallowing of air, or aërophagia.

When patients suffering from cardiac or gastric disease experience relief after belching gas, they are tempted to repeat the process; but in order to do this more air must be swallowed. In this way a habit of aërophagia is developed. It is evident, therefore, that while attacks of aërophagia are in themselves of a functional character, some other cause than a pure neurosis may be present. Particularly is this true of organic disease of the stomach or heart, where symptoms may be relieved by the removal of gas from the stomach.

Retention of Gas.—Severe and continued attacks of gaseous eructation are usually due to aërophagia. In some patients, however, the gas swallowed is not entirely returned through the mouth. It may pass on into the intestines and cause marked abdominal distention. Possibly also, in some cases, the excess of gas may remain in the stomach and may play a part in causing acute or chronic gastric distention.

Esophageal Diverticula

Two types of localized esophageal dilatation unattended by stenosis may be distinguished according to their modes of origin: (1) those arising from traction outside of the esophagus, traction diverticula; and (2) those arising from pressure within, pressure or pulsion diverticula.

Traction Diverticula.—The former are caused most frequently by the traction of scar tissue about old inflammatory processes. They usually occur in the neighborhood of the bifurcation of the trachea and are most commonly due to old tuberculous glands in this neighborhood. As a rule diverticula of this type are small and of a conical shape. They rarely cause disturbances in the mechanism of deglutition, and they derive their chief clinical significance from the fact that they may give rise to perforations of the esophagus.

Pressure Diverticula.—Pressure diverticula arise most frequently at the posterior junction of the pharynx and esophagus, which junction is at the level of the cricoid cartilage. At this point there seems to be a physiological weakness of the muscle wall, and the strain to which it is subjected during swallowing produces the diverticulum. The walls of such diver-

ticula usually contain very few muscle fibers, thus suggesting that a hernia of the mucosa and submucosa has taken place through the muscular layer. These diverticula frequently grow to a considerable size, and they may produce a marked interference with deglutition. When food enters the sac the adjacent esophagus is compressed and the opening into the esophagus at the mouth of the sac becomes closed. The food swallowed then passes almost entirely into the sac. From here it may be regurgitated or it may be expressed by pressure on the side of the neck. Since the closure of the esophagus is largely a matter of chance, the interference with swallowing usually varies greatly from time to time. At times even coarse food passes down the esophagus, while at other times even liquids are caught in the diverticulum and obstruct the esophageal canal.

Disturbances of Gastric Secretion

Physiological Considerations

After food has been swallowed, the greater portion remains in the stomach for a variable period of time, being held by the closure of the pyloric and cardiac sphincters. At first it is acted upon by the diastatic ferment of the saliva that is mixed with the food in the mouth, and is then swallowed with it. After the contents of the stomach have been rendered acid by the gastric juice, however, the activity of the salivary ferment is inhibited, and the contents are then subjected to peptic digestion. The food in the stomach may also be acted upon by bile and pancreatic juice that may at times regurgitate back from the duodenum, but as a rule the acidity of the gastric contents prevents any effective digestion by the ferments in these secretions.

Stimulants to Gastric Secretion

Rehfuss, Bergeim and Hawk have recently shown that the normal human stomach is not empty in the morning, but that it contains a not inconsiderable quantity of gastric juice (30 to over 100 c.c.), which usually contains both free hydrochloric acid and pepsin. Carlson has also shown that there is a continuous secretion of juice into the human stomach, even though the latter contain no food. This secretion may be accelerated either by nervous or by chemical influences.

(*a*) *Nervous Secretion*

The brilliant work of Pawlow and his school emphasized the important part played by nervous influences in furnishing an initial stimulus to gastric secretion. The mere act of chewing and swallowing appetizing food is shortly followed by a profuse flow of gastric juice; and this hap-

pens even though the food, instead of entering the stomach, leaves the body through an esophageal fistula. The nervous impulses that cause this initial secretion are carried to the stomach by the vagi, and if these nerves be cut no neurogenous secretion follows the eating of food. The vagus stimuli to gastric secretion take their origin mainly from reflexes which arise in the special sense organs of taste and smell. Chewing, smelling or even seeing appetizing food starts a neurogenous secretion of gastric juice. Probably also the secretion may be initiated by psychic processes, for Bogen taught a child to associate the taking of food with a certain sound, and he was able to produce a flow of juice by this sound. The presence of an appetizing meal, therefore, causes not only a flow of saliva, but also an analogous, though less marked, increase in the flow of gastric juice.

Thus we have a physiological basis for the belief that the flow of gastric juice is favored by appetizing and agreeable surroundings at the table. Anger and other unpleasant emotions certainly interfere with digestion. That they disturb the secretion of gastric juice was demonstrated by Bickel in a striking manner. This observer established a gastric fistula in a rather irritable dog, and he found that the neurogenous flow of juice could be suddenly stopped when anger was induced. by bringing a cat into its presence.

(*b*) *Chemical Secretion*

The second stimulus to gastric secretion occurs after the food has entered the stomach. Mechanical irritation of the mucous membrane apparently plays little or no part in provoking this flow of juice. It is due to the chemical effect of certain foods or of their digestive products. Among these effective substances are water, the extractives from meat, alcoholic liquors, and the products of protein and starch digestion. In the case of some of these, at least, the stimulus to secretion is not a direct one, but is due to substances which pass into the blood stream and from there act on the secreting cells. Thus Edkins and Tweedy found that when meat extractives, dextrose or dextrin were applied to the isolated duodenum or pyloric region of the stomach, they caused a secretion to be poured out from the fundus glands of the stomach, whereas they were ineffective when applied to the fundus itself. Apparently, therefore, substances which are formed or absorbed at the pyloric end of the stomach or the duodenum may stimulate the fundus cells to increased activity. It has been noted that the administration of an enema may increase the gastric secretion, and this may also be due to the absorption of some stimulating substance.

Properties of the Gastric Juice

Among the more important constituents of the gastric juice are hydrochloric acid, the ferments and mucus. Hydrochloric acid plays an impor-

tant rôle in all the gastric activities. It excites reflexes which close the lower end of the esophagus against the regurgitation of gastric contents, and it plays an even more important part in controlling the activities of the pyloric sphincter. It converts the gastric proferments into the active enzymes. In the stomach hydrochloric acid renders powerful assistance in digesting proteins, and it is said by A. Schmidt to assist in the digestion of certain forms of cellulose. In the duodenum it is one of the factors that call forth the secretion of pancreatic juice and of bile. Finally, the acidity of the gastric contents inhibits bacterial growth, and thus protects the body and the intestines to some extent against the entrance of harmful bacteria.

Pepsin.—Pepsin is the gastric ferment which digests proteins. It is most active in an acid medium, being particularly effective in the presence of hydrochloric acid. It splits up the proteins by a process of hydrolysis into simpler nitrogenous compounds, the peptones and proteoses, which are characterized by the fact that they are less easily precipitated than the original proteins. Its action upon connective tissue is relatively important, because the latter, unlike most proteins, is not readily attacked by the pancreatic trypsin.

Chymosin or Rennin.—The gastric juice also contains a ferment which coagulates milk, and which is known as chymosin or rennin. The coagulation of milk delays its exit from the stomach, and so favors its gastric digestion.

Lipase.—A fat-splitting ferment, lipase, has been frequently demonstrated in the gastric contents. Lipase often enters the stomach owing to a regurgitation of the duodenal contents, but it seems probable that, in addition, the gastric mucosa secretes a lipase. Up to the present, however, but little is known of pathological variations in the amount of this ferment.

Secretion of Mucus.—The mucus of the gastric contents is derived in part from that swallowed with the food. In addition mucus is secreted by special cells of the gastric mucous membrane which are most numerous in its pyloric portion. The secretion of mucus is entirely independent of the secretion of hydrochloric acid and ferments. While the latter show similar variations under pathological conditions, the mucus is often increased when the acid and ferments are diminished or absent. The gastric mucus appears to act as a mechanical protection to the mucous membrane. It neutralizes to some extent the hydrochloric acid and it aids in forming a suspension of solid particles in the chyme.

Hyperacidity and Hypersecretion

The acidity of the material removed from the stomach after a test breakfast is estimated by titrating with a decinormal alkaline solution. The results are expressed in figures which indicate the number of cubic centimeters of the alkaline solution that are required to neutralize 100 c.c. of gastric contents. After a test breakfast the acidity thus expressed usu-

ally does not exceed 60 (0.22 per cent HCl) for the total acidity and 45 (0.17 per cent HCl) for the free hydrochloric acid. Somewhat higher total acidities are obtained after a full meal. By hyperacidity in the clinical sense we mean that the titration figures are above the normal.

Acidity of Pure Gastric Juice.—A hyperacidity of the gastric contents is not necessarily due to a corresponding increase in the acidity of the secretion poured out by the mucous membrane. Pure gastric juice, obtained from a fistulous opening into a normal stomach and not mixed with food, always shows a much higher acidity than is normally found in gastric contents, the total acidity of pure juice ranging from 93 (0.35 per cent) to 150 (0.56 per cent). The cause of the difference between the acidity of pure juice and the acidity of gastric contents that are recovered after various test meals lies partly in the dilution of the gastric juice by the liquids of the food taken, and partly in the neutralization of the hydrochloric acid by the alkaline saliva, the alkaline gastric mucus, and above all, according to Boldyreff, by neutralization with the alkaline pancreatic juice that regurgitates through the pylorus into the stomach. In conditions of clinical hyperacidity we never meet with figures which exceed the limits of normal acidity for pure gastric juice.

It is evident, therefore, that while hyperacidity of the gastric contents may possibly be due to the secretion of a more acid gastric juice, it may also be caused by the secretion of unusual quantities of a normal gastric juice or by a failure on the part of some of the agencies that normally dilute or neutralize the gastric contents. The clinical differentiation of these various factors is not easily made; but animal experimentation as well as observations on men with gastric fistulae has shown that pure gastric juice possesses an acidity which is rarely approached and never exceeded by the gastric contents in conditions of hyperacidity. It seems probable, therefore, that the latter is due not to the secretion of an unusually acid juice, but to the secretion of a normal juice in excessive amounts or to an insufficiency in some of the neutralizing factors.

Hypersecretion.—In practice it is customary to define gastric hyperacidity as a condition in which the gastric contents, though approximately normal in quantity, show a high acid content. In what is called hypersecretion, on the other hand, the gastric contents are increased in amount without an evident pyloric obstruction.

Relation of Hyperacidity to Gastric Motility

The mechanism which governs the rate at which the gastric contents are discharged into the duodenum will be discussed in later sections of this chapter. It may be mentioned here, however, that gastric hyperacidity is not infrequently associated with some delay in the emptying of the stomach. More fluid than usual is often obtained after a test meal, and the x-ray examination may also show that the final emptying of the stomach is

delayed. This delayed emptying apparently depends in part upon the secretion of large amounts of juice, and in part upon an increased activity of the pyloric sphincter, which delays the passage of gastric contents into the duodenum.

Effect of Hyperacidity on Gastric Digestion

In hyperacidity the gastric contents become acid more promptly than usual. This shortens the period during which starch can be digested by the salivary ferment that enters the stomach. Since, however, the main digestion of starch normally takes place in the intestines, this can hardly lead to any serious impairment of starch digestion.

As a result of the stronger acidity, and possibly also owing to some delay in the emptying of the stomach, the digestion of proteins may be more complete than usual. This again appears to have but slight significance from the standpoint of general digestion, unless indeed the over-digestion plays some rôle in the pathogenesis of the constipation that is relatively common in patients with hyperacidity. Hyperacidity is of clinical interest partly because it is relatively frequent in certain organic diseases within the abdominal cavity, and partly because it is a direct or indirect cause of certain gastric symptoms.

Symptoms of Hyperacidity

Hyperacidity may be present without clinical manifestations or it may be accompanied by a more or less characteristic group of symptoms. Among the latter are an ill-defined feeling of gastric distress, definite gastric pain, burning sensations beneath the sternum and eructations of acid fluids. These symptoms are most intense at the height of digestion; i. e., between one and three hours after a meal. They are usually relieved by alkalis, such as sodium bicarbonate and magnesia, which serve to neutralize the excess of acid in the stomach.

Contributory Factors.—A trustworthy diagnosis of hyperacidity cannot be made from the symptoms alone. At times a patient with complaints that suggest gastric hyperacidity shows subacidity or anacidity on gastric analysis. Furthermore, the gastric symptoms do not parallel the degree of acidity. Certain persons who have never had a gastric complaint show hyperacidity on analysis, while others with characteristic symptoms may show a normal or only slightly increased acidity. It seems necessary to assume that other factors than the percentage of hydrochloric acid influence the character and the severity of the symptoms that are usually attributed to hyperacidity. Among these assumed factors we may mention a general hypersensitiveness on the part of the patient or a hyperesthesia of the stomach itself. It is certain that the symptoms of hyperacidity often accompany general nervousness, yet it is possible that the

immediate cause of the symptoms is not a hypersensitiveness alone, but that there may be accompanying disturbances in the motor functions of the stomach. The pain, for example, may be due to pyloric spasm, while the acid burning and acid eructations may be due to an insufficiency of the cardiac sphincter which permits the gastric contents to enter the lower esophagus. If such motor disturbances play a rôle in producing symptoms, the absence of a definite parallelism between symptoms and the degree of acidity may be readily understood.

Constipation.—Constipation is relatively frequent in patients with gastric hyperacidity, but the relation between the two is by no means clear. On the one hand, as we have pointed out, the hyperacidity, by favoring an overdigestion of the food and a consequent reduction in the fecal residue, may predispose to constipation. On the other hand, the disturbed intestinal motility may possibly produce a reflex hyperacidity.

Causes of Hyperacidity

Hyperacidity more than any other disturbance of gastric secretion is apt to be accompanied by no manifest lesions of the mucous membrane lining the stomach. Such a "functional" hyperacidity is particularly frequent in young individuals and in those of a nervous temperament. Certain persons suffer from the symptoms of hyperacidity whenever they are placed under an unusual nervous strain, and those who follow occupations that involve much care and worry are especially liable to symptoms of this type. There is, therefore, clinical evidence that hyperacidity symptoms may be caused by psychic influences.

Nervous Reflexes.—These symptoms may also be caused by nervous reflexes that originate in organic disease of the abdominal viscera. They are not uncommon, for example, during pregnancy and in those suffering from chronic appendicitis, gall-stones and chronic constipation. When the primary disease is cured, such patients may be entirely relieved of their gastric symptoms. Since the gastric secretion is stimulated in part by impulses that descend through the vagi nerves, it is obvious that under pathological conditions there may be an excessive nervous stimulation, which would account for the psychic and reflex types of hyperacidity.

Altered Gastric Mucous Membrane.—Other types of gastric hyperacidity are manifestly due to an irritation or disease of the mucous membrane of the stomach. The occasional or habitual use of highly seasoned food, the hasty swallowing of coarse food, smoking, alcoholic excesses—all these may irritate the gastric mucous membrane and produce a hyperacidity of the gastric contents. The hyperacid form of gastritis is closely related to such irritative factors. Finally, hyperacidity is relatively common in certain gross anatomical lesions of the stomach, especially chronic ulcer.

Hypersecretion

Hypersecretion in the clinical sense is distinguished from hyperacidity by the fact that in absence of any evident obstruction at the pylorus unusual quantities of liquid material are obtained from the stomach. Two forms have been described. In the intermittent type the hypersecretion recurs at irregular intervals, and is associated with severe pain and vomiting. In the other type, called chronic gastrosuccorrhea, or Reichmann's disease, the hypersecretion is continuous. Even though the stomach has been emptied the night before, large quantities of secretion unmixed with food may be obtained in the morning. The quantity that must be obtained in order to constitute hypersecretion is not definitely known. It is frequently stated that not more than 20 c.c. of fluid should be obtained from the fasting stomach, but Rehfuss and his associates found 100 c.c. or more in certain normal individuals. The fluid recovered from the stomach in cases of hypersecretion usually contains a large percentage of hydrochloric acid.

Methods of Recognition Inadequate.—While it seems probable that cases of marked hypersecretion actually exist, it must be admitted that our methods for recognizing the condition are rather inadequate. On the one hand, the normal fasting stomach may contain a considerable amount of liquid and acid secretion. On the other, a slight pyloric stenosis or a pyloric spasm may interfere with the normal emptying of a normal fasting secretion, and thus increase the residue obtained in the morning aspiration. It is certain that many cases of supposed hypersecretion are caused by organic disease of the stomach, and particularly by unrecognized gastric ulcers.

Achlorhydria and Related Conditions

We have seen that an increased percentage of hydrochloric acid in the gastric contents is not necessarily due to a hyperacid secretion, but that it may be, and usually is, due to the secretion of excessive juice, lack of neutralization or alterations in gastric motility. A marked diminution in the percentage of hydrochloric acid, on the other hand, usually indicates a lessened secretion of acid. This diminution of acid is frequently associated with a diminution in pepsin and chymosin. As a general rule, the ferments are normal or diminished in conditions of subacidity, while they are diminished or absent in achlorhydria. To this rule, however, there are exceptions, and in some cases of achlorhydria the pepsin is diminished to a greater extent than is the acid. When hydrochloric acid is absent from the gastric contents the condition is called achlorhydria. When acid and ferments are both absent, it is called an achylia gastrica. In the latter condition, therefore, no active gastric juice is secreted. Yet the mucous membrane may still be able to secrete liquids and mucus, for no definite

relation exists between the secretion of acid or ferments and the secretion of mucus. In certain cases of achlorhydria, indeed, the mucous membrane produces excessive quantities of mucus; in others, the amount of mucus is normal or diminished.

Relation to Gastric Motility

When the stomach of a patient with achlorhydria is aspirated after a standard test breakfast it is a common experience to find that little or no material can be recovered, and that the water used for lavage is returned clear. The main portion or perhaps the whole of the test breakfast has left the stomach at a time when the normal stomach should contain a residue of from 75 to 100 c.c. Furthermore, Cohnheim, who has studied the rate of gastric discharge in animals by means of a duodenal fistula, observed that in a dog which had a gastric catarrh with achlorhydria the meat eaten passed through the pylorus with unusual rapidity. Achlorhydria is, therefore, frequently associated with a rapid emptying of the stomach. The cause of this hypermotility will be discussed later, but it may be pointed out here that it seems to be due to an absence of the duodenal reflex which normally closes the pylorus when the acid contents of the stomach enter the duodenum.

Effect on Gastric and Intestinal Digestion

Inspection of the residue recovered from the stomach of a patient with achlorhydria usually shows a noticeable lack of digestion. The food appears to have been simply chewed and mixed with mucus, and undigested solid particles adhere to one another, instead of being separated and more or less disintegrated as in the normal gastric contents.

Protein digestion is reduced or absent. The lack of gastric acidity increases the opportunities for the digestion of starch in the stomach by means of the salivary ferment that has been swallowed with the food; but when, as often happens, the food passes rapidly into the duodenum, little time is allowed for starch digestion in the stomach.

Increased Work of Intestines.—It is obvious, therefore, that achlorhydria markedly lessens the digestion of food in the stomach and throws an added amount of work upon the intestines. The powerful ferments encountered in the intestines are usually able to compensate for the lack of gastric digestion, and as a rule no excessive loss of nutrient material by way of the feces takes place. Only in the case of animal connective tissue does the gastric juice appear to possess peculiar digestive properties, and in patients with achlorhydria masses of tough meat may escape digestion and appear as such in the stools. Compensation by the intestines for an absent gastric digestion also takes place when the entire stomach is removed by a surgical operation. Although such a removal may be followed for a time

by disturbances of digestion and absorption, these processes later become quite normal despite the absence of a stomach.

The extra strain thrown upon the intestines by gastric achlorhydria may, in certain cases, lead to intestinal disturbances. Patients with achlorhydria not infrequently complain of constipation, intestinal gases, foul-smelling feces, and diarrhea. Particularly characteristic of achlorhydria is the tendency to diarrhea. This may be continuous, or it may occur in attacks that are separated by shorter or longer intervals. While diarrhea does not occur in a very high percentage of such patients, nevertheless it is an important symptom, for the reason that other forms of chronic diarrhea are rare in temperate climates. In achlorhydria imperfectly prepared food is being constantly emptied into the intestines. The coarse character of this food may cause some mechanical irritation. More important, however, is the fact that undesirable decompositions take place in the intestines, partly because of the unusual quantity of undigested material, and partly because the absence of gastric acidity permits the entrance of an unusual number and variety of microörganisms that have been swallowed with the food. The intestines become irritated by these decomposition products or by the abnormal bacteria flora.

Symptoms of Achlorhydria

A considerable number of patients with gastric achlorhydria complain of no symptoms whatsoever and the condition is only discovered when the stomach is pumped. Others complain of indefinite gastric disturbances, such as loss of appetite, distress after meals and eructations. Still others complain of the intestinal disturbances that have just been enumerated. Finally, many suffer from various nervous complaints that are not directly attributable to the gastro-intestinal canal.

Nervous Changes.—The relation between achlorhydria and general nervousness is an interesting one. Some authors have attributed the achlorhydria to nervous influences (achylia gastrica nervosa). As we shall see, however, it is highly improbable that nervous changes should in themselves produce a permanent lack of gastric secretion, such as is frequently encountered in these patients. A general nervousness may cause a patient with achlorhydria to notice gastric or intestinal symptoms which might otherwise be disregarded. On the other hand, the nervous condition may be in some way a result, and not a cause, of the digestive disturbances. Little definite is known concerning the effects of abnormal intestinal decompositions upon the body, but it seems quite possible that such decompositions may affect the nervous health, and that this may cause certain general symptoms that occur in patients suffering from the intestinal complications of achlorhydria. In some cases the nervous symptoms disappear when the effects of the achlorhydria are corrected by a proper diet and the administration of hydrochloric acid. Rarely, however, does any method

of treatment cause a return of the normal gastric secretion in patients who have once shown achlorhydria on several examinations.

Causes of Achlorhydria

Of fundamental importance in discussing the etiology of achlorhydria is the question as to its nervous origin. We have seen that Pawlow and later physiologists demonstrated that the secretion of gastric juice was markedly influenced by nervous impulses. The first portion of the gastric secretion is certainly due to such stimuli, and Bickel showed that this neurogenous secretion could be suddenly checked by angering his dog. It is tempting to assume that chronic achlorhydria is also due to such nervous influences. It should be remembered, however, that the gastric secretion may also be excited by chemical stimuli, and it is very doubtful if the chemical secretion can be checked by central nervous influences. Experience with patients has shown that while a certain amount of variation in the gastric analyses may be attributed to psychic or other nervous influences, and while these variations tend to be more marked in neurotic individuals, nevertheless complete absence of hydrochloric acid can rarely be attributed to transient nervous disturbances. For example, achlorhydria does not come and go with the relapses and remissions of manic-depressive insanity; nor, again, with the fluctuations of health that occur so frequently in patients suffering from functional neuroses. Furthermore, achlorhydria, once definitely established, usually persists even though the general nervous health of the patient improves.

Changes in Gastric Mucous Membrane.—It has long been known that certain cases of achlorhydria are due to demonstrable anatomical changes in the gastric mucous membrane. Faber and his associates have shown, further, that in the great majority of patients with achlorhydria anatomical changes may be demonstrated. They believe that these changes are of an inflammatory character, and they have, therefore, concluded that most cases of achlorhydria are due to chronic gastritis. Even when no anatomical changes are found, it is quite as probable that the disturbed secretion is due to chemical changes in the cells as that it is due to nervous influences. Faber also believes that many patients, in whom the hydrochloric acid is diminished but not absent, are suffering from a relatively mild form of chronic gastritis.

Old Age.—We have said that achlorhydria is usually a chronic disease from which recovery rarely takes place. Since it is not particularly dangerous, it is evident that it will be more common in elderly persons; for once having developed, it continues indefinitely. In this way the frequency of the condition among elderly persons is probably to be explained.

Pernicious Anemia.—Achlorhydria is common in association with certain diseases. In pernicious anemia, for example, it occurs almost invariably. The usual anatomical changes in the mucous membrane are also

found in this disease. It seems certain that the anemia itself does not cause the absence of gastric secretion, for the latter may be absent years before the anemia develops, and it remains absent even when the blood picture during a remission appears almost normal. Then, too, other equally profound anemias, clinical as well as experimental (Minami), may be associated with no diminution in the gastric secretion. On the other hand, it is possible that the achlorhydria may in some way contribute to the etiology of pernicious anemia, but the relation is evidently not a simple one, for patients with achlorhydria may have no anemia at all or they may have a simple secondary anemia.

Gastric Carcinoma.—Achlorhydria is a common but not an invariable manifestation of gastric carcinoma. This type of achlorhydria appears to be due not alone to a diminished secretion, but also in part to an excessive neutralization of acid that has been secreted by the stomach. (See Gastric Carcinoma.)

Infections.—In addition to these there are the so-called idiopathic achlorhydrias, in which no immediate cause for the condition is apparent. The chronic gastritis in such patients is commonly attributed to an abuse of the stomach with alcoholic drink, indigestible food or hasty eating. Analyses of clinical records, however, suggest that the condition is due not infrequently to infectious causes. Typhoid fever, in particular, appears to be rather frequent in the past history of such patients.

Excessive Secretion of Mucus

It has been pointed out that gastric mucus is secreted by other cells than those which secrete the acid and ferments of the gastric juice, and that under pathological conditions no fixed relation exists between the two processes. An excessive secretion of mucus may occur with normal, diminished, or even, in some cases, with increased acidity. The occurrence of excessive quantities of mucus in the gastric secretion has been regarded as a pathognomonic sign of gastritis, and it certainly indicates a catarrhal condition of the mucus cells lining the stomach. The significance of such a gastric catarrh, however, is uncertain. On the other hand, chronic gastritis in the anatomical sense may be present even though there be no marked excess of mucus. This may happen, for example, in achlorhydria.

Disturbances of Gastric Motility

Physiological Considerations

Cardiac Sac.—In man the stomach normally has a J or fish-hook form and lies mostly to the left of the median line, with its lower border at about the level of the umbilicus. From the physiological standpoint it may be

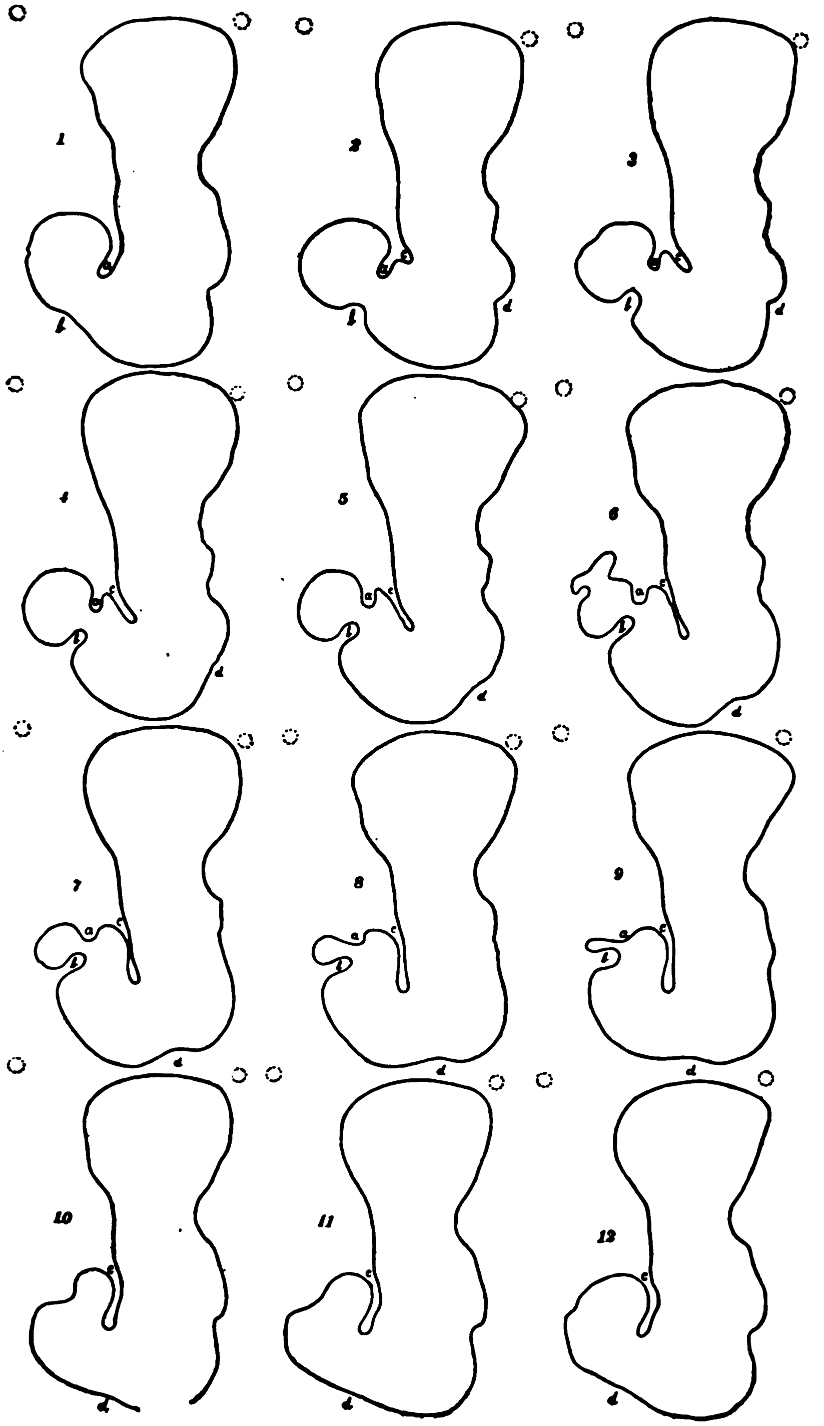


Fig. 56.—Kinematographic Records of the Gastric Outlines in Man Showing the Progress of the Peristaltic Waves *a*, *b* and *c*, *d*. (From Kaestle, Rieder and Rosenthal, Arch. Röntgen Ray.)

divided into two portions, which have been called by Cunningham the cardiac sac and the gastric tube. The cardiac sac, or upper half of the stomach, receives the food coming from the esophagus and contracts upon it with a fairly constant pressure, despite variations in the amount of its contents. The degree of contraction is spoken of as the gastric tone. When the tone is normal the gastric contents do not simply collect at the lowest portion of the stomach, but they are held up to a fairly constant level. When more food is taken, the level rises but slightly, and the stomach accommodates the increased quantity by increasing its diameter (Fig. 58). The cardiac sac acts mainly as a reservoir for holding the food, and under normal conditions it shows few if any peristaltic movements. If the food swallowed is solid or semisolid, it remains quiet so long as it is in the sac, and when various foods are fed in succession they tend to form layers in this portion of the stomach. The earlier layers lie toward the pylorus and along the greater curvature, while the later layers lie along the lesser curvature (Groedel).

Gastric Tube.—The second or pyloric half of the stomach is called by Cunningham the gastric tube and it is the seat of the most marked peristaltic activity. It may be free of peristalsis for considerable periods of time even when it contains food. When peristalsis occurs, the waves usually originate on the greater curvature at, or somewhat above, the middle of the stomach, and from this point they pass slowly toward the pylorus. As the wave proceeds forward along the greater curvature it gradually becomes deeper and soon an indentation appears directly opposite on the lesser curvature. This double constriction moves up to the pylorus but it never passes beyond that point. In man peristaltic waves arise at the rate of about three (two to four) per minute and as they progress very slowly it frequently happens that two or more waves may be observed at the same time along the gastric tube (Fig. 56).

The lumen of the pyloric portion of the stomach is rarely, if ever, completely closed off by the waves that sweep over it. So long as the pylorus is closed, the peristaltic waves serve simply to mix and churn the gastric contents in this portion of the stomach. Cannon has watched small solid particles containing a bismuth salt move forward toward the pylorus as a peristaltic wave approached, and then back again as the wave passed by.

From time to time a portion of the gastric contents is allowed to escape through the pyloric sphincter. The loss of material from the gastric tube is made up from that which is stored in the cardiac sac. Thus the amount in the latter region is gradually reduced until, finally, the last of the gastric contents has been passed on into the duodenum (Fig. 57).

The Control of the Pylorus

The pyloric sphincter controls the rapidity with which material is discharged from the stomach. Although peristaltic waves reach this

sphincter at the rate of from two to four a minute, the latter allows material to escape only at intervals which vary in length from ¼ of a minute to several minutes. When material is allowed to escape through the pylorus,

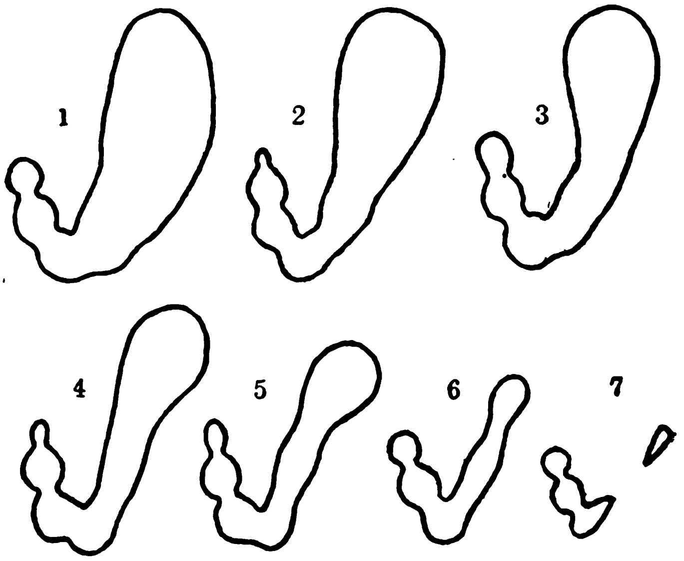


Fig. 57.—Tracings of the Shadow Cast by the Cat's Stomach at Hour Intervals After a Meal. Note that as the Stomach Empties the Cross Diameter of the Fundus Diminishes With (at First) But Little Change in Its Length. (From W. B. Cannon, "Mechanical Factors of Digestion," published by Longmans, Green & Co.)

it does so in little squirts which show that a considerable pressure is maintained in the pyloric tube.

Control of Rate of Exit.—Two main factors govern the rate at which the pyloric orifice allows food to leave the stomach. According to Cannon, opening of the pylorus is favored by the action of the acid gastric contents upon the mucous membrane lying proximal to the pylorus. Any food which lessens the secretion of gastric juice (fats) or which binds the acid secreted (proteins) will, therefore, tend to delay the opening of the pyloric sphincter. Carbohydrates leave the stomach rather promptly, because while they cause a secretion of gastric juice they do not bind the acid.

The second mechanism which controls the pyloric sphincter is excited when the acid gastric material comes in contact with the mucous membrane lining the duodenum. This causes a reflex closure of the pylorus behind the material that has passed into the duodenum. Only after the duodenal acidity has been neutralized by the bile and the pancreatic juice is the pylorus free again to respond to the opening stimulus that arises from the mucous membrane on its proximal side.

Three Main Motor Activities.—It is evident, therefore, that gastric motility in its wider aspects consists of three principal functions: (1)

the constant force with which the stomach contracts on its contents, i. e., its *tone;* (2) the frequency, depth and force of the *paristaltic movements* that pass over the distal half of the stomach; and (3) the *pyloric control* of the passage of gastric contents into the duodenum.

The term gastric motility has been used by clinicians to designate the rapidity with which the food leaves the stomach. Although this usage has the advantage that it indicates a definite and important function of the stomach, it should be remembered that gastric motility in the clinical sense has little to do with the force and frequency of gastric peristalsis. The peristaltic waves, for example, are often markedly increased in cases of pyloric obstruction when the exit of food from the stomach is delayed. On the other hand, in achlorhydria the peristaltic waves may be normal, even though the stomach empties itself with unusual rapidity.

Gastric Motility in Secretory Disturbances

We have already noted the fact that in the majority of patients with achlorhydria comparatively little material is recovered when the stomach is pumped at the usual time after a test breakfast. The cause of this rapid exit of gastric contents may now be discussed. According to Groedel, the tone of the stomach in such patients is, as a rule, not less than the normal. The first swallows of food do not fall rapidly to the bottom of the stomach and the stomach appears to contract firmly upon its contents. The frequency and depth of the peristaltic waves that pass over the stomach are also normal or are slightly lessened. The hypermotility depends, therefore, upon changes in the action of the pyloric sphincter. We have seen that the latter is normally controlled by the acidity of the material on either side of the pylorus. In achlorhydria, where this acidity is absent, one might suppose that on account of the lack of acid on the gastric side of the pylorus the sphincter would open late, and the exit of food would be slow. It appears, however, that the lack of acid on the duodenal side is a more important factor in this case. As a result of this lack of acid, the reflex closure of the pylorus, which normally takes place when the gastric contents reach the duodenum, is diminished or absent and material passes out of the stomach with unusual rapidity.

Gastric hyperacidity, as we have pointed out, is probably due to an increased secretion of normal juice rather than to the secretion of an abnormally acid juice. It is not surprising, therefore, that a somewhat increased amount of material can often be obtained on pumping the stomachs of such patients. Not only does the increased secretion of gastric juice tend to increase the residue but there is probably, in addition, some tendency on the part of the pyloric sphincter to hold material back in the stomach on account of an increase in the acid duodenal reflex. Cannon has shown experimentally, that while a certain amount of acid in the gastric contents favors the exit of food from the stomach, an excessive amount

delays its exit, probably on account of this action upon the duodenum. The relatively slight increase in the amount of material recovered from most cases of hyperacidity indicates that no very marked pyloric spasm is present in these patients.

Gastric Atony

Nature of Atony

By gastric atony or lack of gastric tone is meant a condition in which the muscular wall of the stomach fails to contract with normal force upon its contents. The conception of atony is a definite one, but its clinical recognition and its effects upon gastric physiology have been subjects of much discussion. It has been claimed, for example, that in the absence of an organic pyloric obstruction a dilatation of the stomach or a delay in emptying its contents may reasonably be attributed to a weakness of the muscle walls. It now seems certain, however, that such changes are quite as often due to changes in the activity of the pyloric sphincter or to changes in the secretion of the gastric juice. The lax condition of the stomach wall in gastric atony has been said to favor the occurrence of splashing sounds when the abdominal walls are suddenly moved. Stiller and others have regarded such succussion sounds as important evidence of atony.

X-ray Examination of Atonic Stomach.—Since the advent of the x-ray, new data for the diagnosis of gastric atony have been obtained by observing the manner in which the stomach fills when the patient swallows a bismuth meal before the fluoroscopic screen. According to Groedel, the atonic stomach shows the following peculiarities when examined in this manner: (1) the first material swallowed drops promptly to the bottom of the stomach instead of being held for a short time in its upper portion; and (2) as food is taken it continues to collect at the bottom of the stomach, so that this organ, instead of having a roughly cylindrical form, becomes pear-shaped. Indeed, the stomach may even appear to have a constriction across its midportion which disappears on having the patient lie down (Fig. 58).

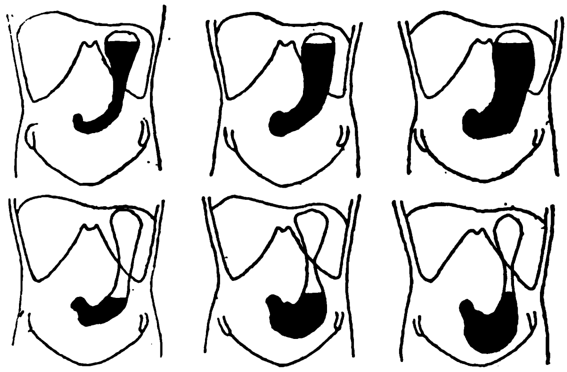


Fig. 58.—Diagrams Showing the Filling of the Normal, Orthotonic Stomach (Upper Line) and of the Atonic Stomach (Lower Line). Note that in the Latter the Material Tends to Sink to the Lower Part of the Stomach and Depresses Its Lower Border. (Redrawn from Hertz, Brit. Med. Jour.)

According to Holzknecht, even these x-ray signs of gastric atony

are not reliable, for they may be present when the abdominal wall is abnormally lax and they can be made to disappear when the wall is voluntarily contracted.

Effect on Gastric Position

The relation of atony to the size and position of the stomach is also a complicated one. Since atony tends to be associated with a weak gastric muscle, it favors the occurrence of dilatation and particularly of a dilatation and sagging at the lower end of the stomach where the food collects. Yet neither dilatation nor a low position of the stomach is in itself characteristic of gastric atony. Some enlarged stomachs possess a normal or increased tone, and particularly is this the case in the earlier stages of pyloric obstruction when moderate dilatation may be associated with muscular hypertrophy. Nor is a low position of the stomach characteristic either of dilatation or atony, for in certain individuals the stomach is naturally low, and this gastroptosis may not cause any symptoms nor be associated with any signs of atony.

Effect on Gastric Motility

The peristaltic movements of the atonic stomach may be normal or they may be diminished, thus giving a combination of atony and deficient peristalsis. In the milder types of atony the emptying of the stomach is normal. When, however, the atony is marked, there is a delay in the expulsion of food from the stomach. Rarely if ever, however, is this delay so marked that food remains in the stomach over night. The latter condition is almost invariably due to an organic obstruction at the pyloric orifice. It is obvious, however, that the milder grades of delayed emptying may be due either to organic or functional causes.

Etiology of Atony

Atony may be caused by a primary weakness of the stomach wall or it may be a secondary effect of pyloric stenosis. Such stenosis causes at first an increased peristalsis with hypertrophy of the muscle wall of the stomach, but eventually it causes a weakness of the muscle with dilatation and atony.

A primary muscular weakness may be associated with other organic disease of the stomach, and chronic gastritis, for example, is sometimes accompanied by atony of the muscle. More often, however, the primary form of gastric atony appears as part of a general weakness, and especially in association with malnutrition, anemia, tuberculosis, fever, or general splanchnoptosis.

Pyloric Obstruction

Causes

Pyloric obstructions may be divided into two general classes: those due to *anatomical* and those due to *functional* narrowing of the pylorus. To the former group belong the stenoses caused by carcinoma, by cicatricial ulcers and by perigastric adhesions that are secondary to gall-stones, ulcers, and appendicitis. The degree of constriction produced by such organic narrowings varies from those which hardly interfere with the passage of the gastric contents to those which cause an almost complete closure of the exit into the duodenum.

Functional Stenosis.—The second or functional type of stenosis is due to a spasm of the pylorus. This may be produced by reflexes that arise from gall-stones, from chronic appendicitis or from other abdominal disease. Organic disease at or near the pylorus is a frequent cause of spasm, and particularly is this true of pyloric and prepyloric ulcers. Pylorospasm may also be due to the action of a hyperacid gastric contents on a normal or hypersensitive mucous membrane in the stomach. Finally it may be due to certain drugs (morphine).

The spastic forms of pyloric obstruction do not usually cause a very serious delay in the emptying of the stomach, but they do cause some delay, and not infrequently they are responsible for severe cramplike pains in the epigastric region.

Effect on Motility

In the earlier stages of a pyloric stenosis there may or may not be a definite delay in the emptying of the stomach. In consequence of the obstruction, the tone of the stomach and the peristaltic movements may be so increased that the stomach empties itself within the normal time limits despite the obstruction. As the obstruction progresses, however, it becomes more and more difficult for the stomach to empty itself with its usual speed. If it be examined one hour after a test breakfast it is found to contain more than the normal amount of material, and if it be examined seven hours after a full meal it may still show a residue from the meal taken, whereas a normal stomach should be approximately empty at this time. Similarly if a bismuth meal be taken, x-ray examinations show that the exit of bismuth from the stomach is delayed.

Degree of Motor Insufficiency.—It is customary to classify the degree of delay according to whether or not the stomach usually succeeds in emptying itself over night. If the gastric motility is distinctly diminished but the stomach discharges its contents during the night, it is called a motor insufficiency of the *first degree*. Such a condition may be due to atony, pylorospasm, or to a mild organic obstruction. If the stomach fails to

empty itself over night, the condition is called a motor insufficiency of the *second degree*. In such a case, the stomach is rarely if ever completely free of food residue, and the conditions are peculiarly favorable for the growth of microörganisms with decomposition of the gastric contents. This more serious type of motor insufficiency is rarely due to any cause other than a marked organic obstruction at the pylorus.

Increased Peristalsis.—We have seen that during the earlier stage of pyloric obstruction the delay in the emptying of the stomach is insignificant. At this stage, the tone of the gastric muscle is usually well-preserved and the peristaltic movements are increased. On inspecting the abdomen of such a patient the powerful contractions of the stomach can often be seen through the abdominal wall. After a variable period of relaxation there appears to be a general tonic spasm of the entire stomach, the so-called stomach stiffening, and this is usually succeeded by a succession of deep peristaltic waves that pass from left to right across the gastric shadow. Such an appearance occurs only in cases of organic obstruction at the pylorus. Fluoroscopic examination also shows well-marked peristaltic waves which may be two or three times as deep as normal. Antiperistaltic waves have been occasionally observed in such patients and, when present, they usually indicate an advanced organic obstruction.

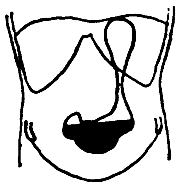


Fig. 59.—Diagram Showing the Filling of a Dilated Atonic Stomach Caused by Pyloric Obstruction from Ulcer. (Redrawn from Hertz, Brit. Med. Jour.)

Dilatation of Stomach.—Sooner or later the stomach fails to empty its contents to such an extent that dilatation sets in. The stomach, dilated from pyloric obstruction, appears to be unusually broad on fluoroscopic examination (Fig. 59). The dilatation causes a loss of muscular tone and the retained liquids sink to the bottom of the stomach. When fresh bismuth-containing food is swallowed, it can be seen dropping like tar through the fluid already in the stomach. As a rule the peristaltic movements persist even when considerable dilatation is present. They may begin higher than usual and progress with deep furrows toward the pylorus. Sometimes, however, the peristaltic waves appear to be absent even when there is marked retention and a fair gastric tone (Barclay).

Acute Dilatation of the Stomach

This rare and remarkable condition occurs most frequently after operations, especially laparotomies; less commonly during the course of infectious diseases, particularly pneumonia, as well as after injuries and in association with various wasting diseases and nervous lesions. It may even occur during perfect health. Clinically, it is characterized by the acute onset of vomiting, abdominal pain, distention and tenderness. There is great thirst and scanty urine, and in many instances the patient rapidly

passes into a condition of collapse which terminates fatally within a few days. The persistent and profuse vomiting is the most common and important symptom. The vomitus is usually thin and watery and is frequently bile stained, brownish or black. Only exceptionally is it feculent. Free hydrochloric acid may or may not be present in the vomitus.

At autopsy the most striking finding is an enormously dilated stomach wihch may occupy almost the entire abdomen. In a considerable proportion of the cases there is also a dilatation of a part or of the whole of the duodenum, and in some of the patients this dilatation stops abruptly at the point where the duodenum passes beneath the insertion of the mesentery, at which point there may be a definite obstruction of the duodenum by the tensely stretched mesentery. Below this obstruction the intestines are collapsed.

Pathogenesis.—Three chief explanations have been offered for the mechanism which leads to acute dilatation of the stomach. The first of these attributes the dilatation to a primary obstruction of the duodenum at the point where it passes beneath the insertion of the mesentery. At this point the duodenum passes between the spinal column and aorta behind, and the mesentery of the small intestines with the superior mesenteric artery in front. If the spinal column at this point is prominent and particularly if the mesentery with its contained artery is drawn taut, the mechanical conditions are favorable for such duodenal obstruction. Tension on the mesentery is increased if the small intestines are empty and are located in the pelvis, and if, at the same time, the mesentery is so short that the intestines in this position cannot be supported by the floor of the pelvis. If acute gastric dilatation were due solely to such an abstruction one would expect an early increase in the peristaltic movements of the stomach. Only in the late stages should peristalsis cease and marked dilatation occur. As a matter of fact only a very few of the reported cases of acute dilatation have shown increased gastric peristalsis at any time. In most patients visible peristalsis has been entirely absent throughout the disease. In such cases there must have been a marked loss of muscular activity from the time that the symptoms began.

Second Theory.—The second explanation offered for acute gastric dilatation is, that it is due to an acute hypersecretion of gastric juice. Enormous quantities of liquid can usually be recovered from the stomach. It is improbable that all this fluid is due to gastric secretion, however, for the percentage of acid is usually low, and free hydrochloric acid is often absent. The presence of bile in the fluid suggests that fluid has regurgitated back from the duodenum.

Third Theory.—The third explanation offered for acute dilatation is that it is due to an acute loss of tone in the gastric wall. The absence of visible peristaltic movements indicates that such a loss of tone is always present and their absence from the start in many cases suggests that this is

the primary cause of the dilatation. Experimentally, a diminution in the peristaltic movements of the stomach and intestines, and a delay in the emptying of the stomach may result from anesthesia, and from cooling or handling of the intestines. Resection of the vagus nerve also diminishes the movements of the stomach and may lead to gastric dilatation. Various acute toxic influences seem to have a similar effect.

Lack of Gastric Tone.—We see, therefore, that the lack of gastric tone is the most prominent feature of this type of dilatation. It is possible that it occurs secondarily to a duodenal obstruction and that it is caused by a reflex from the duodenum. It is also possible that it is primary and that the mechanical obstruction of the duodenum at the point where it passes beneath the mesenteric attachment results from a crowding of the intestines into the lower abdomen by the distended stomach. In any case, a vicious circle tends to become established; the dilatation of the stomach increases the duodenal obstruction, and the latter tends to increase the gastric dilatation. Favorable therapeutic results have sometimes been obtained when these mechanical factors were combated by repeatedly aspirating the contents of the stomach and by attempting to relieve the obstruction by having the patient lie on the abdomen or by assuming the knee-chest position.

Vomiting

Mechanism

Vomiting is usually preceded by the sensations of nausea. The individual feels weak and prostrated, he becomes pale, a cold perspiration breaks out, and there is an increased flow of saliva and of the mucous secretions from the mouth and the bronchial mucous membranes. The pulse becomes weaker, and the respirations more rapid and irregular.

The gastric movements during vomiting have been carefully studied in intact animals by Cannon and others. Before emesis actually takes place, the pyloric region becomes tightly closed. In cats deep contractions proceed from the midportion of the stomach to the pyloric region and they completely close off the lumen of the stomach just before the pylorus is reached. In dogs, according to Hesse, the antral region of the stomach becomes tightly closed without the occurrence of marked peristaltic waves. At the same time, the tone of the remainder of the stomach lessens and the cardiac sphincter relaxes. During the deeper respirations that now occur, the gastric material, as shown in dogs by Hesse, enters the lower esophagus through the relaxed cardiac sphincter and this material may move up and down with each respiration.

Finally, by a contraction of the diaphragm and a simultaneous spasmodic contraction of the abdominal muscles, the intra-abdominal pressure is markedly raised and the contents of the stomach are thrown out through

the esophagus into the mouth. If the closure of the larynx and of the nasopharynx is imperfect, material may find an exit through the nose or it may enter the air passages and provoke a paroxysm of coughing. The stomach itself seems to play only a passive part in the actual ejection of the gastric contents. After a portion has been vomited the stomach contracts firmly on the contents that remain. Antiperistaltic movements are usually absent during vomiting. At the end of emesis, material may still remain in the stomach and the esophagus. The latter, however, is returned to the stomach by esophageal peristalsis. At the conclusion of the vomiting, a sense of relief is experienced, but the muscular weakness may continue for some little time.

Causes of Vomiting

The act of vomiting is governed by a nervous center that lies in the medulla oblongata. During vomiting centrifugal nervous impulses pass from this center to the stomach by way of the vagus nerves, to the diaphragm by way of the phrenic nerves and to the voluntary muscles of the abdominal wall by way of the spinal cord and spinal nerves.

Direct Excitation of Nervous Center.—Vomiting may be excited by a direct excitation of this nervous center either by mechanical or by chemical stimuli. Increased intracranial pressure is an important cause of vomiting, acting through a mechanical stimulation of the center. Local disease of the medulla and pons are said to be particularly prone to cause vomiting. Various drugs act in whole or in part upon the vomiting center. Among these are apomorphin, the digitalis bodies, tartar emetic, etc. The vomiting of uremia and the pernicious vomiting of pregnancy are believed to be due in part to the action of poisonous substances upon the vomiting center. A certain type of periodic vomiting in childhood, that which is associated with an unusual formation of acetone bodies, also appears to be due to the action of toxic substances upon the center.

Reflex Excitation.—The center may also be acted upon by reflexes. Thus abnormal impulses from the internal ear may produce vomiting when there is disease in this region or when, as in seasickness, a series of nervous stimuli occur in the semilunar canals owing to the rapid changes in the position of the body. Reflex vomiting frequently takes its origin from the abdominal organs, as in gastritis, gastric stasis, inflammations of the appendix and peritoneum, during biliary and renal colic, etc. Irritation of the pharynx at about its juncture with the esophagus may also cause reflex vomiting.

Changes in Higher Cerebral Centers.—Finally, vomiting may be produced in susceptible individuals by changes in the higher cerebral centers. Thus some individuals become nauseated and may even vomit when unpleasant subjects are discussed. Unpleasant odors frequently have a

nauseating effect and may lead to vomiting. The vomiting of migraine also appears to arise from changes in the higher cerebral centers.

Continual Vomiting

Vomiting that occurs occasionally is an unpleasant but not a very serious symptom. Continuous vomiting may be due to a persistence of the original cause; but, in addition, individuals of a nervous temperament tend to establish a vomiting habit owing to the development of an easy reflex path. Under such circumstances even slight external stimuli may start a paroxysm of vomiting.

Constant vomiting leads to malnutrition, partly through the actual loss of food material from the stomach, but mainly because the lack of appetite and the fear of vomiting curtail the intake of food. In some cases the vomiting is so constant that even liquids cannot be retained. When vomiting is severe and continuous, the vomitus eventually becomes bile stained owing to a regurgitation of the duodenal contents into the stomach. Finally, continued vomiting leads to constipation on account of the partial starvation.

Gastric Motility after Gastro-enterostomy

It has frequently been assumed that if an opening be made between the most dependent portion of the stomach and a loop of small intestines the gastric contents will drain out of the stomach through this new opening. Cannon has pointed out, however, that this simple conception of drainage of the stomach does not correspond with the actual conditions in the stomach and abdomen, at least when the pylorus remains patent. In the first place, the conditions in the abdominal cavity, so far as drainage of the stomach is concerned, should not be compared with a filled stomach, which is held in the air and from which fluid can escape through any opening in its dependent portion. The stomach is surrounded with intestines and other abdominal contents of about the specific gravity of water, and the conditions are more comparable with a stomach suspended in water than with one suspended in air. It is evident that, under these conditions, the contents will not drain from the most dependent portion but must be moved on by the contractions of the gastric muscle. The peristaltic waves which pass from the midportion of the stomach toward the pylorus tend, therefore, to move the gastric contents in the direction of the natural exit from the stomach rather than toward an artificial opening in its most dependent portion. Furthermore, digestion is most advanced in the distal portion of the stomach, and when solid food has been taken the gastric contents in this distal portion are more fluid and are, therefore, more readily carried forward.

Intact Pyloric Opening.—Observations both on animals and on men

have shown that, so long as the pyloric opening is intact, the products of gastric digestion are usually emptied through the pylorus rather than through an artificial opening in the lower part of the stomach. Kelling established a duodenal fistula in animals and observed that after gastro-enterostomy the material usually passed through the pylorus. Failures to close a duodenal fistula by simply performing a gastro-enterostomy have permitted Berg to make similar observations on man. X-ray examinations of animals after gastro-enterostomy by Cannon and Blake have also shown that if the pylorus be intact the food almost invariably escapes from the stomach through the normal exit, rather than through the new operative opening. Even when the pylorus has been artificially narrowed but not entirely occluded, food often continues to pass through the narrowed orifice.

Obstructed Pylorus.—The practical surgical importance of these experimental and clinical observations is at once apparent. Gastro-enterostomy cannot be relied upon as a drainage operation when the pylorus and the gastric musculature are normal. Only when there is a definite obstruction at the pylorus is there a reasonable prospect that the new opening will afford a physiological short circuit into the intestines. It is well known that the most brilliant therapeutical results of this operation have been obtained in just this class of patients. In conditions of marked atony, and particularly when there is a marked atonic dilatation, the mechanical conditions in the stomach may differ from the normal to such an extent that the new opening may at times functionate. At least gastro-enterostomy occasionally benefits such patients, although the benefit is neither so constant nor so striking as when the dilatation is due to a pyloric obstruction.

From the physiological standpoint, also, it is evident that when a gastro-enterostomy is performed it is advantageous to make the new opening as near the pylorus as possible, for in this region the gastric contents are more fluid, the peristaltic waves are more marked and the pressure is higher. A pyloroplasty is the ideal operation for a pyloric stenosis, although for practical purposes it may not be the operation chosen.

Return of Intestinal Contents to Stomach.—Not only may a gastro-enterostomy opening fail to act as a short circuit between the stomach and the intestines, but it may permit the return of intestinal contents into the stomach. The gastric contents which have passed the pylorus, the duodenum and proximal jejunum, may reënter the stomach when they reach the operative opening, or, again, material from the stomach may enter the proximal loop of intestines directly from the stomach and then be returned by the peristaltic movements of this portion of the intestines. The former condition is called a vicious circle. Apparently, it occurs not infrequently after gastro-enterostomy but it seems to be less serious than is usually supposed. At least in the experimental experience of Cannon and Blake, the serious symptoms following gastro-enterostomy were invariably due not to a vicious circle but to a kinking of the intestine below the anastomosis.

Peptic Ulcer

Peptic ulcers occur only in those portions of the gastro-intestinal tract that are exposed to the action of the gastric juice. They occur most commonly in the stomach or duodenum but they may also occur in the jejunum near a gastro-enterostomy opening and in the lower end of the esophagus. In the stomach, peptic ulcers most frequently involve the posterior wall, the lesser curvature and the pyloric end of the stomach, though any portion of the stomach may be affected. In the duodenum they occur just distal to the pylorus and are very rare beyond the point where the alkaline bile and pancreatic juice enter.

Peptic ulcers may be acute, subacute or chronic. The most characteristic are the chronic ulcers. These usually show on examination a punched-out or funnel appearance, with the diameter of the deeper portion less than the diameter of the more superficial portion. Often the diminution in diameter is by a succession of terraces. Peptic ulcers may be irregular in shape or they may be round or oval. Frequently they are multiple. Microscopically there is, as a rule, little evidence of acute inflammation about the base, but the latter becomes markedly indurated in chronic ulcers and in healing much scar tissue may be formed which later contracts and leads to strictures and deformities.

Pathogenesis

The distribution of peptic ulcers indicates that they are due to a digestion of the tissues by gastric juice. Before further discussion of their pathogenesis, therefore, it becomes necessary to inquire why the gastric juice normally fails to digest the wall of the stomach. Not only is such digestion very rare, but even when lesions of the mucous membrane have been produced by various means these usually heal with great rapidity, so that at the end of two or three weeks the normal conditions are reëstablished. Obviously some mechanism exists in the gastric mucous membrane which causes it to resist peptic digestion.

Resistance of Living Tissue to Digestion.—John Hunter believed that the resistance to digestion was a general property of all living tissue. Since his time this question has been frequently studied, and the results of these studies indicate that the degree of resistance to gastric digestion varies considerably in different tissues. For example, the leg of a living frog as well as the ear of a living rabbit may be digested by gastric juice. On the other hand, the living gastric wall even when denuded of its mucous membrane or when denuded of both mucous and muscular coats offers a considerable resistance to gastric digestion. The same is true of portions of the intestines as well as of the living spleen. In order that these struc-

tures should resist digestion, however, it is necessary that a good blood supply be maintained.

The mechanism of this resistance to digestion is not finally settled. So far as the gastric mucous membrane is concerned, all are agreed that a certain amount of protection is afforded by the presence of mucus on its surface, and it has been pointed out that in patients with gastric ulcers the amount of mucus recovered from the stomach may be less than normal. But it is also obvious that, while the presence of mucus may afford some protection, it cannot be the chief factor that confers immunity against peptic digestion upon other living tissues than the gastric mucous membrane.

Action of Antiferments.—Weinland showed that intestinal parasites resist digestion within the intestinal tract by virtue of the fact that they contain an antiferment which neutralizes the ferments to which they are exposed. Similar antipeptic and antitryptic substances have been isolated from the mucous membrane of the stomach and upper intestines and from the mucus covering its surface, and it seems not improbable that the living tissue, and particularly these portions of the digestive tract, may owe a part of their immunity to the possession of these antiferments. Katzenstein has, indeed, attempted to show that the development of peptic ulcers is due in part to a disturbance of the relation that should exist between the ferments and antiferments of the stomach and duodenum.

Oxidation of Active Ferments.—More recently Bunge has observed that while proferments resist destruction by an electric current, active ferments are easily destroyed by this means, and he believes that the destruction is due to oxidation. On the basis of these observations, it has been suggested that the immunity of living tissue to digestion depends upon its ability to oxidize and thus destroy the active ferments. The inactive proferment in the gland resists such destruction, but once it has left the gland and has been converted into the active ferment it is readily oxidized when it comes in contact with living tissue. In this way living tissue may protect itself against digestion.

Relation to Gastric Secretion

We have seen that the gastric juice plays an essential part in the production of peptic ulcers, and the question therefore arises, whether an increased acidity of the gastric juice is a common or an essential factor in the pathogenesis of ulcer. Statistics have shown that fifty per cent or more of patients suffering from ulcer have an increased amount of hydrochloric acid in the gastric contents, and this has led some to attribute the ulcer formation to an abnormal activity of the gastric juice. Yet hyperacidity may occur without ulcer, and it is by no means constant in those with ulcer. Not infrequently there is a normal acidity, while

in some patients there is a subacidity. Schryver and Singer believe that in duodenal and pyloric ulcers the hydrochloric acid and the peptic activity of the gastric juice are increased, whereas in ulcer of the body of the stomach the hydrochloric acid varies and the peptic activity of the juice is usually diminished.

Hyperacidity.—Even when unusual quantities of acid are found in the gastric contents of ulcer patients, it is by no means certain that this hyperacidity precedes the formation of the ulcer. Hyperacidity may be caused by reflexes from various organic diseases within the abdominal cavity, and among these by reflexes from gastric or duodenal ulcerations. Schryver and Singer suggest, also, that the excess of gastric secretion in duodenal and pyloric ulcers may be due to an excessive formation in these regions of those chemical substances which normally excite gastric secretion (page 139). It is quite possible, therefore, that the hyperacidity associated with ulcer is a secondary manifestation rather than a cause of the ulcer.

Abnormal Susceptibility of Mucous Membrane.—While the digestive activities of the gastric juice play an essential part in the pathogenesis of ulcer and while ulcers probably never develop if the gastric secretion is absent, nevertheless, there is no reason to believe that hyperacidity is an essential factor in ulcer formation. If other conditions are favorable the normal gastric juice can digest the wall of the stomach, and although an excess of acid or of pepsin may favor this digestion it is not necessary for ulcer formation. The essential change that leads to ulcer must lie in some condition which renders the mucous membrane abnormally susceptible to the action of the gastric juice. Some of these factors will now be considered.

Vascular Disease

Of the factors which create a loss of resistance to digestion, one of the most important is a disturbance in the blood supply to the stomach wall. Since the time of Virchow, attention has been directed repeatedly toward this possibility. Attempts to produce ulcers *experimentally* by ligating the arteries entering the stomach wall have usually met with failure, probably because there are numerous arterial anastomoses within the various layers of the stomach wall. More success, however, has attended efforts to block the finer gastric vessels by injecting small particles in suspension, or by injecting coagulating substances into the gastric arteries. In particular Payr has, in recent years, injected dilute formalin and other irritants into the gastric vessels and in this manner has produced experimental ulcers in the stomachs of rabbits, guinea-pigs and dogs, which resembled those occurring naturally in man.

Vascular Changes in Man.—The localized character and the funnel shape of gastric ulcers in man suggest a vascular origin, and Hauser,

teristic of a chronic gastritis, such as Faber has described in other forms of achlorhydria.

It is evident, however, that an absence of gastric secretion is not the sole cause of the achlorhydria in cases of gastric carcinoma. In some cases considerable hydrochloric acid must be added before the contents give a reaction for free acid. Furthermore, the amount of secreted chlorids and the amount of total acidity may indicate that considerable hydrochloric acid has been secreted by the stomach even when none is present as free acid. Evidently the gastric contents in such cases contain an unusual amount of substances which neutralize free acid. These substances are of a nitrogenous character and they may be derived from the tumor secretions, from the proteins of the food or from cleavage products of these proteins in the stomach.

Excessive Cleavage of Proteins.—It has been pointed out by Emerson and others that proteins may undergo an unusually complete cleavage in the stomachs of patients suffering from gastric carcinomata. The normal gastric juice splits proteins to proteoses and peptones but is unable to carry the disintegration to the final stage of amino acids. On the other hand, carcinomatous tissue, in common with extracts from various organs of the body, contains ferments which decompose peptones and polypeptids into amino acids. Within recent years many efforts have been made to utilize this fact in the diagnosis of gastric carcinoma. From the practical standpoint various difficulties are encountered in applying this test, such as the necessity for excluding a possible action of ferments swallowed in the saliva or of ferments that have been regurgitated from the duodenum. Despite these practical difficulties, however, such studies have strengthened the belief that in carcinoma of the stomach ferments are frequently present in the gastric contents which are able to disintegrate peptones and polypeptids. Cleavages of this type increase the acid binding properties of a given amount of protein, for with each cleavage more amino groups become available for acid combinations. The unusual binding properties of the gastric contents in certain cases of carcinoma of the stomach, therefore, depend in part upon the fact that there has been an excessive cleavage of proteins taken into the stomach.

Lactic Acid.—Lactic acid fermentation of the gastric contents is common in patients suffering from carcinoma of the stomach. It is most marked when a carcinoma at the pylorus produces a motor insufficiency of the second degree. Under such circumstances the stomach fails to empty itself over night and fermentative microörganisms are given an opportunity to grow continuously in the gastric contents. Long nonmotile bacilli (Oppler-Boas bacilli) may be found in great number in the stagnating gastric contents. These bacteria produce lactic acid when grown outside of the body, and they are doubtlessly responsible for the lactic acid that is found in cases of obstructive carcinomata. Their con-

tinuous propagation is permitted by the fact that the stomach does not empty itself at least once in the twenty-four hours. A second factor requisite for their development is a lack of free hydrochloric acid. Stasis in the presence of free hydrochloric acid does not permit the growth of these bacilli. It is evident, therefore, that one would expect to find lactic acid fermentation and the Oppler-Boas bacilli in any condition in which a serious organic obstruction at the pylorus is associated with achlorhydria. This combination is, however, very rare except in the case of obstructing carcinomata. For this reason, the presence of lactic acid and Oppler-Boas bacilli are of considerable value in the diagnosis of carcinoma. They may also be present in carcinomatous stomachs which show no marked obstruction. In such cases it is not improbable that the bacilli are harbored in the crevasses of the tumor although it is also possible that lactic acid may be produced by some specific ferment of the tumor.

Gastric Sensations

Appetite, Hunger and Repletion

In a normal individual the only sensations ordinarily referable to the stomach are the sensations of hunger, of appetite, and of repletion during the course of a meal. These sensations normally guide the individual in the selection of the kind and quantity of food taken, and they are so delicately adjusted to the needs of the body that the body weight ordinarily varies but little under varying conditions of nutritive demands and nutritive supply. The regular intake of even a slight excess of nourishment, over and above the actual needs of the body, will in time produce a marked increase of weight. This rarely occurs in normal individuals, however, for the reason that a sudden gain in weight is normally succeeded by a diminished desire for food. Conversely a sudden loss in weight is normally succeeded by an increased desire for food. It seems probable, therefore, that the fundamental control of these sensations lies in the state of body nutrition.

Possibly the sense of repletion that develops during the course of a meal is due in part to an increase in the intra-abdominal or the intragastric pressure. Neisser and Brüning state that they have observed rapid emaciation follow tight lacing of the abdomen and rapid recovery follow a correction of this habit. The gains in weight that frequently succeed child bearing are possibly due to the relaxed condition of the abdominal muscles.

Loss of appetite and early repletion during a meal are common symptoms in certain nervous individuals. Less common is an excessive appetite or an absence of the sense of repletion. The cause of these deviations from the normal is not known.

Appetite and Hunger Different Sensations.—The sensations of appe-

tite and of hunger are so intimately associated with each other, that some observers have held that they are but quantitative differences of a single sensation, appetite being a mild form of hunger. It now seems certain, however, that the two sensations are essentially different. Hunger is a dull, gnawing or aching sensation that is intermittent and is referred to the epigastrium or lower sternum. It is often associated with lassitude, drowsiness, faintness, headache and inability to work. Appetite, on the other hand, is more intimately connected with the sense of pleasure in eating. It may be dissociated from hunger, as where one eats a delectable dessert with appetite, though not because one is still hungry, or where on account of great hunger one eats a food that is naturally distasteful or even nauseating.

Hunger Contractions.—The observations of Cannon, Carlson and their collaborators have demonstrated that intermittent hunger sensations are associated with intermittent contractions of the empty stomach and especially of its pyloric end. Each of these contractions usually lasts from twenty to thirty seconds, and they follow each other at varying intervals which may in some cases be so short that a tetanic contraction of the stomach results. So far as we know, similar contractions do not accompany the sensation of appetite. Hunger contractions may be temporarily inhibited by a variety of conditions, such as chewing, stimulation of the nerves of taste, swallowing movements, the entrance of various liquids into the stomach, violent exercise, smoking a strong cigar, etc.

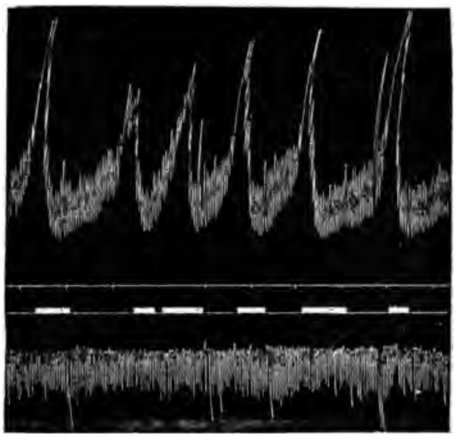


Fig. 60.—Record of Hunger Contractions of the Human Stomach. The Rises on the Upper Tracing Indicate the Contractions. The Signal Marks Below Record the Sensations of the Individual. (From W. B. Cannon, "Bodily Changes in Pain, Hunger, Fear and Rage.")

In General Diseases.—In *infectious* diseases the hunger contractions appear to be diminished, a fact which doubtlessly plays a part in the lack of desire for food that occurs in such patients. On the other hand, when a dog has been rendered *diabetic* by the removal of the pancreas the hunger contractions are usually pronounced, despite the general prostration and the asthenia of the voluntary muscles that accompany the advanced malnutrition of these animals.

In Duodenal Ulcer.—Patients suffering from duodenal ulcer and related conditions not infrequently experience a pathological type of hunger pain. In addition to the dull gnawing sensations with weakness and inability to work, which characterize the condition of hunger in normal

individuals, these patients suffer from acute distress, or more or less actual pain that comes on some time after the food has been eaten. Like the normal type of hunger, however, this pain is relieved by the taking of food. Such pathological hunger pains may occur in a variety of gastric conditions, but they seem to occur particularly in conditions associated with gastric hyperacidity and especially in duodenal ulcer. Such pains have frequently been attributed to an excess of hydrochloric acid in the gastric contents, but they have been observed at times in patients with subacidity or even anacidity. While the exact relation of such pains to the contractions of the stomach has not been definitely determined, it is noteworthy that they are most frequently associated with duodenal ulcer, in which condition, as we have seen, gastric hypertonus, increased gastric peristalsis and early gastric hypermotility are common. The early exit of food from the stomach, combined with a tendency to excessive motor activity, probably accounts for the unusual severity of hunger pains in these patients.

Gastric Pain

The mucous membrane of the stomach is insensitive to tactile stimuli, even though considerable mechanical injury be produced by cutting, pinching or pricking. It is relatively insensitive to thermic and to chemical stimuli. The introduction of 0.5 per cent hydrochloric acid into a normal stomach, or into a stomach that is the seat of an ulcer, causes no pain. Hertz also found that when a strong alcoholic solution enters the stomach it causes merely a feeling of warmth, whereas when it is allowed to act upon the lower end of the esophagus it produces burning sensations. It is evident, therefore, that the pains encountered frequently in gastric ulcer, and less frequently in conditions of simple hyperchlorhydria, must be due to some cause other than the action of a relatively high concentration of acid on the normal or eroded mucous membrane.

Increased Tension of Muscle Wall.—Provided there is no disease of the peritoneum, gastric pains appear to be caused mainly or solely by the muscular contractions of the walls of the stomach or by their mechanical distention. In other words, gastric pain is caused by an increased tension of the muscle wall. Thus Hertz produced pain by a rapid distention of the stomach. In gastric dilatation secondary to pyloric obstruction the pains present when the stomach is distended are often promptly relieved when the gastric contents are evacuated by vomiting or by a stomach tube. During the spasmodic "stomach stiffening" observed in such patients some pain may be felt. Finally, during fluoroscopic examinations various observers have noted that pain may be experienced when spasmodic contractions occur either near the pylorus or in the body of the stomach, even though the cause of the spasm is located at some distance. Thus a peristaltic wave may pass over an ulcer in the body of the stomach

without causing pain, whereas on reaching the pyloric region it may cause a pylorospasm and with this considerable pain. It seems evident, therefore, that one and probably the most important cause of gastric pain is an increased tension of the muscular elements of the stomach wall. In peptic ulcer and in gastric hyperacidity the changes in gastric motility and especially the spasm of the gastric muscle must often depend in some way upon the acid of the gastric contents, for these pains are frequently relieved by the administration of alkalis.

Involvement of Peritoneum.—A second cause for gastric pain is an involvement of the peritoneum. The layer of peritoneum which covers the stomach, like that which covers the intestines, appears to be insensitive to tactile stimuli, whereas the parietal peritoneum is very sensitive. Peritoneal inflammation or peritoneal adhesions probably produce pain through an involvement of the parietal layer. Perigastric adhesions, for example, may produce pain by traction on the parietal peritoneum. This traction may occur immediately after the ingestion of food and be related to the quantity rather than to the quality of the food taken; or again the pains due to the adhesions may be associated with the various motor activities of the stomach. It is possible, furthermore, that the pain experienced during gastric distention or during spasm of the stomach wall may be due to traction on a normal parietal peritoneum by the mesenteric attachments of the stomach.

Spinal and Other Causes.—The pains that originate in the stomach,

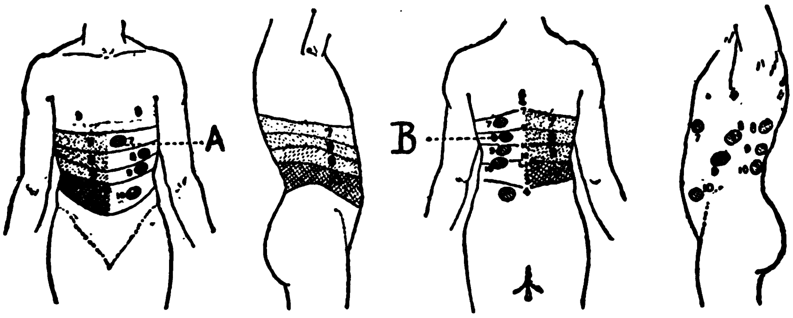


Fig. 61.—Areas of Referred Pain as Given by Head. A Represents One of the Commonest Sites in Front, B One of the Commonest Sites Behind.

like the pains that originate in other viscera, may be referred to the exterior of the body, the peripheral distribution corresponding to the spinal segments that supply sympathetic nerves to the diseased organ. The spinal segments usually affected in gastric disease are the seventh, eighth, ninth and tenth dorsal segments which supply the skin from about the eniform to the umbilicus. It is obvious that pain in this region may also result from disease of the spinal cord or from pressure on or

disease of the corresponding root segments as a result of thoracic aneurism, spinal tumor or spinal inflammation.

The Intestines

Functions of the Small Intestines

When the gastric contents pass into the duodenum a flow of pancreatic juice and of bile is excited. The outpouring of these digestive juices depends upon some action of the hydrochloric acid and of the fat in the chyme upon the duodenal mucosa. Bayliss and Starling showed that if the mucous membranes of the upper intestines be treated with dilute acid or with soaps, an extract can be prepared which will excite a copious flow of pancreatic juice when it is injected into the circulation. The chemical substance that produces this flow is called *secretin,* and it is probably the chief normal excitant of pancreatic activity. The discharge of bile, which follows the entrance of chyme into the duodenum, is due in part to a contraction of the gall-bladder. In part it is due to an increased secretion of bile by the liver, and the latter, like the secretion of pancreatic juice, depends upon the action of secretin formed in the duodenum from the action of chyme upon the mucous membrane.

Control of the Discharge of Chyme.—The entrance of pancreatic juice and of bile into the duodenum influences the rate at which the gastric contents are discharged. We have seen that, when the acid contents of the stomach pass the pylorus and come in contact with the duodenal mucous membrane, they excite a reflex which closes the pyloric sphincter. The alkaline bile and pancreatic juice, on the other hand, neutralize the duodenal acidity and so allow a further discharge of material from the stomach. Through this constantly changing reaction of the duodenal contents there results an intermittent discharge of chyme from the stomach.

Digestion in the Small Intestines.—The main digestion of food takes place in the small intestines. The pancreatic juice furnishes powerful ferments which digest starch (amylase), fats (lipase) and proteins (trypsin). Trypsin is present in the pancreatic juice in an inactive form (trypsinogen). Upon entering the duodenum this zymogen is converted into active trypsin through the action of a substance in the succus entericus to which the name enterokinase has been given. Bile renders important assistance in the digestion of fats. It aids in their emulsification and in the solution of their digestive products. At the same time it markedly accelerates the rate at which the pancreatic lipase breaks up fats into fatty acids and glycerin.

Succus entericus.—The secretion of the mucous membrane of the intestines, the so-called succus entericus, also possesses important digestive

functions. In addition to enterokinase, it contains a number of ferments which attack starches, sugars, fats and the products of proteolytic cleavage. The latter are of particular importance. We have seen that in gastric digestion the proteins are not split beyond the peptone stage. Pancreatic trypsin while less active than pepsin with regard to a few proteins, and particularly the proteins of connective tissues, is in general a more powerful proteolytic enzyme, and it is also able to carry the digestion of proteins to a more advanced stage than can pepsin. Yet the final conversion of the simpler peptones and polypeptids into amino acids is affected mainly by a ferment of the succus entericus known as erepsin. It is this ferment which converts the products of proteolysis into the final products that are absorbed by the intestinal mucous membrane.

Absorption in Small Intestines.—Not only are the small intestines the principal site of digestion but they are also the principal site of absorption. During the passage of material through the small intestine most of the final products of protein, fat and starch digestion, are absorbed. The important digestive rôle of the small intestines is the more remarkable when one considers that the passage through this portion of the alimentary tract takes place normally in from three to six hours.

Functions of the Large Intestines

The material which passes through the ileocecal valve is a thin liquid that has been deprived of most of its nutrient qualities during its stay in the small intestines. Progress through the large intestines is much slower than through the small and during this time water is absorbed from the fecal material, so that it eventually becomes converted into the solid or semisolid feces.

Bacteria in Large Intestines.—In the large intestines there is an enormous increase in the number of bacteria. We have seen that the gastric contents of normal individuals are relatively sterile owing in part to the antiseptic action of free hydrochloric acid, and in part to the regular and complete evacuation of the stomach. The duodenum, jejunum and upper ileum are also relatively free of bacteria. As one approaches the ileocecal valve, however, the number of bacteria in the intestinal contents rapidly increases, and in the large intestines bacteria may make up as much as fifty per cent of the total weight of the dry fecal material. It is fortunate that bacteria are few in the small intestines where food materials are most plentiful. In the large intestines where great numbers of bacteria thrive, digestion and absorption have already removed most of the nutritive material from the intestinal contents.

Bacterial Aid in Digestion.—The bacterial activities in the large intestines may play a part in digesting certain materials which are resistant to the action of the digestive juices poured into the upper small intestines. This is particularly true of cellulose which does not appear to

be attacked by any of the digestive ferments. Herbivora which do not chew their cud (horses, rabbits) decompose no small part of the cellulose taken with the food in the large intestines, and the same appears to be true, though to a less marked degree, in man. To what extent the soluble products of such bacterial activity in the large intestines are available for nutritive purposes is uncertain, though it seems probable that some, at least, are utilized by the organism.

The Exclusion of Pancreatic Juice from the Intestines

Exclusion of the pancreatic juice from the intestines may be due either to an obstruction of the ducts of Wirsung and of Santorini, or to a destruction of the secreting cells of the pancreas.

Effect on Starches.—The effects which follow the exclusion of pancreatic juice from the intestines depend upon the degree to which other digestive juices may carry on digestion. Here as elsewhere in the body there are numerous safety factors, and the loss of a single physiological element may be compensated for to a greater or less extent by the activity of other elements. This fact is particularly evident with respect to the digestion and absorption of starches. Although the pancreatic juice contains a powerful amylase, the exclusion of this juice from the intestines usually interferes but little with the digestion and absorption of starches. Even when the pancreas is totally extirpated from dogs more than half of the starch in the food is usually absorbed, a fact which is all the more remarkable when we recall that in normal dogs diastatic ferments have not been demonstrated in the saliva, in the bile or in the succus entericus in quantities which are usually regarded as of practical importance.

Effect of Pancreatic Excision on Proteins and Fats.—On the other hand, the presence of pancreatic juice is relatively important for the proper digestion and absorption of proteins and of fats. Abelmann and others have shown that when the pancreas is excised a very large part of the fat taken in the food leaves the body in the feces. Instead of the normal loss of about five per cent through the feces, the losses of fat by depancreatized animals may amount to 80 per cent or more. Only when fats are given in natural emulsions, such as that of milk, is there a relatively good absorption, fifty per cent or more being absorbed in some cases. Unusual quantities of nitrogenous material are also lost in the feces after complete extirpation of the pancreas. Fifty per cent or over may escape absorption in place of the small amount of nitrogenous material which is normally excreted through this channel.

Exclusion of Pancreatic Juice in Dogs.—When, in place of excising the pancreas, an attempt is made to exclude pancreatic juice from the intestines of dogs, conflicting results have been obtained. While some investigators, notably Lombroso, found that the digestion and absorption

of fats and proteins was but little affected when the pancreatic ducts were tied or the pancreatic secretions were diverted from the intestines, others found very marked losses of fats and proteins under these conditions. The recent determinations of Pratt, Lamson and Marks, for example, are shown in the following table:

Experiments	Absorption in per cent. of		Remarks
	N	Fat	
Dog 1:			
Experiment 1	..	87.9	At autopsy a sinus was found which carried pancreatic juice into duodenum
Dog 2:			
Experiment 1........	22.2	11.3	Ducts occluded
Dog 3:			
Experiment 1........	88.5	92.2	Before operation
Experiment 2........	23.7	10.0	Ducts occluded
Dog 4:			
Experiment 1........	92.4	91.4	Before operation
Experiment 2........	31.7	44.6	Ducts occluded
Experiment 3........	47.8	63.4	Ducts occluded
Experiment 4........	31.4	76.6	Ducts occluded
Dog 5:			
Experiment 1........	32.1	31.0	Ducts occluded
Experiment 2........	61.7	4.8	Ducts occluded
Experiment 3........	42.4	20.1	Ducts occluded

The cause of the divergent results of different investigators who have attempted to exclude the pancreatic juice from the intestines of dogs is not clear. Pratt and his associates carefully interrupted all the ducts and maintained this interruption by placing a layer of living mesentery between the head of the pancreas and the duodenum. They are inclined to attribute the less striking results obtained by others to imperfect exclusion of the pancreatic secretion from the intestines. In dogs there may be three or four pancreatic ducts and some failures may be due to unligated ducts. Other failures may be due to the formation of fistulous openings between the pancreas and the duodenum after the operation. Possibly also there are individual differences in the animals experimented upon, and some may have a greater capacity than others to compensate for an absence of pancreatic secretion in the intestine.

Effects of Pancreatic Disease.—It is evident from these experiments, however, that marked losses of food material only occur when the exclusion of pancreatic juice from the intestines is complete or nearly complete. It is, therefore, not surprising that few patients even with manifest pancreatic disease show large quantities of undigested food in the feces. Occlusion of the duct of Wirsung alone may be without effect, for in three-fourths or more of all individuals pancreatic juice still

reaches the intestines through the accessory pancreatic duct of Santorini. The patients in whom marked losses of fat and of nitrogenous material have been observed are usually those in whom there has been a widespread destruction of the pancreas from chronic inflammations, especially after calculus occlusion of the ducts, from cysts, or from new growths. Such patients may show marked losses of proteins and fats in the feces. The stools are bulky, soft and often fatty. Microscopically large quantities of undigested muscle fibers with well preserved striae may be found in the stools, and as much as thirty to seventy per cent of the nitrogenous material taken in the food may reappear in the feces. Unusual quantities of fat may also be found in the stools. The feces appear glistening or oily, owing to the presence of neutral fats, soaps and fatty acids, and oil droplets as well as fatty acid crystals may be found microscopically in great numbers. Analyses show that a large proportion, from forty to sixty per cent, of the fat taken in the diet may reappear in the stools. The amount is influenced by other factors, and in particular by the secretion of bile, as well as by the motor, secretory and absorptive functions of the small intestines.

The Cleavage of Fats.—Since pancreatic lipase splits neutral fats into glycerin and the fatty acids, one might anticipate that as a result of exclusion of the pancreatic juice from the intestines, the stools would contain a relatively large proportion of undecomposed fats and a relatively small proportion of the products of decomposition, i. e., fatty acids and soaps. In a few cases such a change has been observed, but as a rule, the relative proportion of fats, soaps and fatty acids in the stools has not been markedly influenced by the exclusion of the pancreatic juice from the intestines. It would seem that the cleavage of fats may be fairly good in the intestinal tract even when the pancreatic juice is excluded. Apparently, however, the cleavage of fats is relatively slow so that it is not completed during the short time that they remain in the small intestines. Since fat absorption normally takes place in this part of the bowel the slow cleavage interferes with absorption. If the cleavage occurs after the intestinal contents have passed the ileocecal valve it may already be too late for proper absorption.

Functional Tests of Pancreatic Secretion.—It is obvious that the changes in the stools which are characteristic of pancreatic disease are found only when the disease is advanced, and that the character of the stool is also influenced by the condition of the intestines and by the presence or absence of bile. Attempts have been made to determine the presence of pancreatic juice in the intestines by the administration of material which is attacked by this juice and by this alone. The digestion of gelatin capsules hardened in formalin (Sahli's test), of muscle or thymus nuclei (Schmidt's test) and of lecithin (Deucher) have been recommended for this purpose. Their value as functional tests of pan-

creatic secretion have been variously estimated. Sahli's test is generally believed to be unreliable. The lecithin test has been used but seldom. Schmidt's test is regarded as the most trustworthy, but its value as a specific indicator of pancreatic deficiency is still uncertain.

Exclusion of Bile from the Intestines

The exclusion of bile from the intestines is usually due to an obstruction of the common bile duct that may result from the impaction of a biliary calculus, from the pressure of a malignant growth or from cicatrices, kinks, etc. The jaundice produced by such obstructions will be considered elsewhere. As might be anticipated from our knowledge of the digestive functions of the bile, an exclusion of this secretion from the intestines has practically no effect upon the digestion and absorption of the carbohydrates and proteins taken in the food. The insignificant changes observed at times in the utilization of these substances may be accounted for by the poor absorption of fats. The exclusion of bile from the intestines affects chiefly the utilization of fats. Unusual quantities of neutral fats, of fatty acids, and of soaps appear in the stools. For example, Fr. Müller found that instead of from 7 to 10 per cent of the ingested fats appearing in the stools, the quantity may rise to 35 or even 75 per cent. Similarly, A. Schmidt found that instead of the normal loss of about 5 per cent on a standard diet, patients with occlusion of the common duct lost about 25 per cent of the ingested fat in the feces. The amounts which appear are influenced by the quantity and kind of fat taken in the diet. If fats are restricted and if those having a low melting point are chosen, the proportion absorbed may approach the normal. Normally, fat particles appear in the blood after giving 40–60 grams of butter. In biliary obstruction these particles do not appear (see Lipemia).

Effect on Cleavage of Fats.—The fats that are present in the feces of patients who have no bile in the intestine are fairly well split into fatty acids and soaps. The lack of bile diminishes the absorption rather than the digestion of fats. When, as sometimes happens, both bile and pancreatic juice are excluded from the intestines, the loss of fats in the feces is exceptionally large.

Clay Color of Feces.—The exclusion of bile from the intestines leads to the characteristic clay color of the feces. This is due in part to the lack of bile pigments, in part to the excess of fat. The increased amount of fats, fatty acids and soaps often gives in addition a glistening appearance to the feces. Microscopically numerous crystalline needles due to the presence of fatty acids and calcium soaps are seen.

Odor of Feces.—The feces during jaundice often have a peculiarly disagreeable odor. It has been supposed that bile acts as an intestinal antiseptic and that the absence of bile causes an increased bacterial

growth and bacterial decomposition in the intestines. Exact studies have shown, however, that the number of bacteria in acholic stools is diminished rather than increased, that the intestinal putrefaction as measured by the amount of conjoined sulphates in the urine is not regularly increased and that no unusual fermentation or putrefaction occurs when the feces are incubated. A. Schmidt suggests that the disagreeable odor of acholic feces is due to the presence of fatty acids, the stools being rancid rather than putrefying.

Disturbances in the Functions of the Intestinal Mucosa

Despite the important part played by the mucosa of the small intestines in the digestion and absorption of food, serious nutritive disturbances are rarely caused by disease of this part of the bowel. This is due mainly to the fact that a wide margin of safety exists in the functions of the small intestines. As much as fifty per cent of the total small bowel may be resected either from dogs or man without fatal results and resections of seventy-five per cent are not necessarily fatal. The animals from which such large amounts have been removed may suffer at first from diarrhea, ravenous thirst and appetite, and a loss of weight. Ultimately, however, they return to a fairly normal condition, the compensatory process being associated with an hypertrophy and hyperplasia of the small intestinal mucosa remaining in the body. On a carefully selected diet such animals usually show little if any loss of food material in the feces. An excess of fat in the diet, however, may cause moderate losses of nitrogen and of fat. It is not surprising, therefore, that localized lesions of the intestines such as occur, for example, in typhoid fever do not ordinarily diminish the utilization of food material.

Effect of Increased Motility.—Lesions of the intestinal mucous membrane are often accompanied by an increased motility of the affected bowel. This tends to increase food losses, for a more rapid passage of material through the small intestines allows less opportunity for the digestion and absorption that normally take place in this portion of the alimentary tract.

Disturbed Absorption of Food Material.—Organic diseases of the small intestines are at times associated with definite disturbances in the absorption of food material. This occurs, for example, in extensive amyloid disease, in which condition there is not infrequently a loss of considerable nitrogenous material and fat in the stools. In widespread tuberculous disease of the intestines and in tuberculosis of the mesenteric glands the absorption of fats may also be definitely diminished, apparently because the lymphatic capillaries are blocked by the tuberculous disease.

Intestinal Fermentative Dyspepsia.—Unusual losses of carbohydrates

in the feces characterize the intestinal fermentative dyspepsia described by Schmidt and Strasburger. In some of these cases the gastric and pancreatic secretions appear to be normal, and the insufficient digestion of carbohydrates is apparently due to an insufficiency of the amylase of the succus entericus. Not infrequently, as H. Meyer and others have shown, the carbohydrate losses are associated with a disturbance in the gastric secretion which may be either a hyperacidity or a hypoacidity, but it is not certain that these disturbances influence intestinal absorption to any noteworthy degree.

Motor Disturbances of the Intestines

Physiological Considerations

The Small Intestines

Movements of the intestines may be observed and recorded after the abdominal cavity has been opened, but it is difficult to be certain that these correspond to the movements present in the intact animal. Studies of the movements in intact animals were first made by Cannon, who examined the abdomen with the x-rays after feeding food which contained bismuth salts. Cannon's observations on animals have been confirmed in the main for man by Hertz, Kaestle and others.

Rhythmic Segmentation.—After entering the small intestines the chyme may remain for a time motionless. When movements occur they are normally of two types. The first of these, described by Cannon as rhythmic segmentation, consists in the sudden division of a given strand of intestinal contents into several short segments of nearly equal size. After a time, each of these segments is divided in the center by a new set of constrictions while the older constrictions disappear. Thus a new series of segments are formed, which overlap the position of the previous set in much the same way that one layer of bricks overlaps the layer next to it. Segmentation then takes place in the new segments and the original pattern is reëstablished. These alternations from one pattern to the next occur quite suddenly. The intervals separating the alternations vary in different animals. In man the changes usually occur at intervals of from six to nine seconds, while the segmenting movements in a given loop of small intestines usually continue for a period of from twenty to sixty seconds (Kaestle).

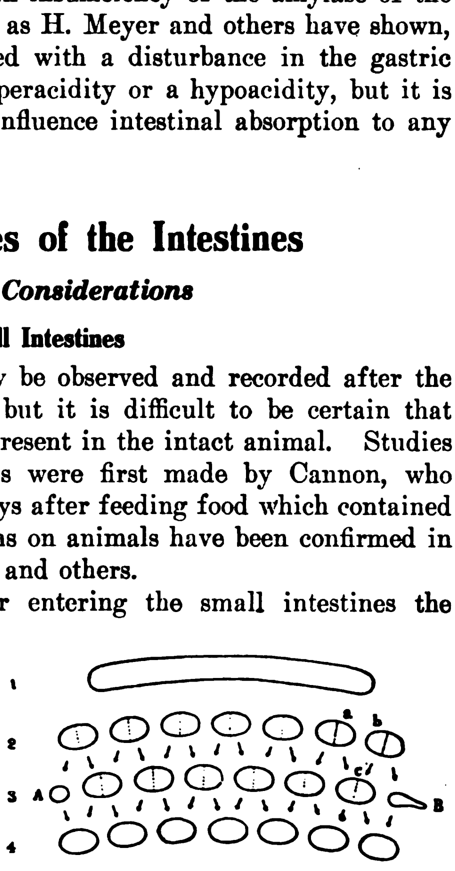


Fig. 61a.—Diagram Representing the Process of Rhythmic Segmentation. (After W. B. Cannon, "Mechanical Factors of Digestion," published by Longmans, Green & Co.)

During rhythmic segmentation the intestinal contents do not undergo any definite translation along the canal. These movements cause a thorough mixing of the food material and the digestive juices. At the same time successive portions of the chyme come in contact with the mucous membrane and absorption is thus favored. Rhythmic segmentation also aids in the propulsion of blood and lymph through the intestinal wall. Rhythmic segmentation is closely related to the movements that are frequently described as pendulum movements, in which the intestinal coils execute gentle swaying movements. These are usually accompanied by rhythmic contractions.

Peristalsis.—The second type of movement seen in the small intestines is that which has long been known as peristalsis. This is characterized by an advancing wave of constriction, preceded by a wave of relaxation. As a result of this combined movement the intestinal contents are swept along the tract in the direction of the anus. The peristaltic movements of the small intestines usually proceed at a slow rate, which Kaestle estimates in man to be something less than one centimeter a second. Furthermore they usually travel only a limited distance (about 12 centimeters). Meltzer and Auer have distinguished in animals another type of peristalsis which may sweep rapidly from one end of the small intestines to the other (peristaltic rush).

Period of Passage in Man.—In a series of plates from two normal individuals, Rieder found that the first portion of a bismuth meal reached the colon in 3½ to 4 hours and that by eight or nine hours the small intestines were empty of bismuth. Taking into consideration the rate at which the stomach evacuates its contents, one may, therefore, roughly estimate the passages of the small intestines in man at from three to six hours. During this relatively brief period nearly all of the available food material is digested and absorbed. The contents that pass through the ileocecal valve are of a watery consistency and contain only a very small amount of nutrient material.

The Large Intestines

In the large intestines the contents lose the greater part of their water, as well as a portion of the nutrient material which has escaped absorption in the small bowel. There is here a marked increase in the number of bacteria, and these, as we have seen, probably cause the considerable loss of cellulose which takes place in this portion of the digestive tract. In herbivora, especially, the cecum and ascending colon are the site of considerable changes, on account of the large amount of cellulose in the diet of such animals.

Three Functional Divisions.—From the functional standpoint the large intestines may be divided into three portions. The first of these

includes the cecum, the ascending colon and the first part of the transverse colon, the second includes the remainder of the transverse colon, the descending colon and upper sigmoid, while the third portion consists of the rectum and lower sigmoid.

Action in First Division.—In the first of these physiological divisions of the large intestines the contents are liquid, and they usually remain here for a relatively long time. Considerable material is usually seen in this portion of the intestines. In cats and other animals, Cannon, Elliott and others have observed antiperistaltic waves sweep from a ring of contraction at about the end of the first third of the transverse colon back toward the cecum. These waves recur at a rate of five or six a minute and they usually continue for a period of two to eight minutes. Such periods of activity are followed by pauses of fifteen minutes or more during which the colon appears motionless. Since the ileocecal valve does not ordinarily permit a regurgitation of the colonic contents into the ileum, the effect of such antiperistaltic movements in the proximal colon is to mix the semifluid contents thoroughly, and to permit a more complete digestion and absorption in this portion of the colon. Antiperistaltic movements of the ascending colon have not been definitely observed in man, yet a number of observations make it clear that in man also the proximal portion of the colon is functionally distinct from that which follows. The intestinal contents remain in this portion for considerable periods of time. Roith has pointed out that when an anastomosis is established between the terminal portion of the ileum and the ascending colon, and when, furthermore, an external fistula is established at or near the cecum, there is a continuous escape of fluid contents and the fistula does not heal readily. If, however, the anastomosis is established at the midportion of the transverse colon, or somewhat beyond this, the external fistula heals readily, and intestinal material is carried toward the rectum.

In apes which possess a large intestine resembling that of man, Stierlin and Fritsche found that reversal of the distal portion of the colon produced definite stasis at the upper end of the reversed segment. Reversal of the proximal portion of the colon, on the other hand, produced no such marked stasis, and the shadows of the intestinal contents passed into the rectum with but little delay. From this observation they concluded that the proximal portion of the colon of apes normally propels the intestinal contents in an oral direction. In man also there is evidently a tendency to stasis in the proximal portion of the colon which may, from analogy with observations and experiments on animals, be due, in part at least, to antiperistaltic movements in this region.

Progress from Proximal Colon to Rectum.—The progress of fecal material from the proximal colon to the rectum has been much discussed. Slow peristaltic waves have been observed on animals, and Rieder by taking a series of x-ray plates at intervals of from one to five minutes was

able to show that slow progressive movements also occur in man. In addition to these slow movements, a number of observers have noted occasional rapid translations of the colonic contents in the direction of the rectum. Holzknecht, who first described these "large colonic movements" in man, believed that three or four such movements, each lasting a few seconds and recurring three or four times in a day, could carry the intestinal contents the length of the large intestines. Hertz and Newton, Case and others, have also observed these large colonic movements in man, particularly after a meal. It is admitted that such movements occur regularly in the descending colon and sigmoid in connection with the act of defecation, but whether they or the slow type of peristalsis are the usual mode of crossing the transverse colon is still uncertain. In this connection it is interesting to note that, while fistulae beyond the middle of the transverse colon discharge soft or solid feces at regular intervals of one to three times a day, fistulae of the proximal colon allow a more or less continuous escape of liquid material.

Haustral Movement.—In addition to antiperistalsis and the two forms of peristaltic movements, a third type of movement has been described in the large intestines. This may be roughly likened to the rhythmic segmentation observed in the small intestines. It is characterized by varying degrees of contraction of the local bands of circular muscle fibers. The haustral sacculations thus produced vary in shape and in depth or at times they disappear entirely.

Defecation.—When material has reached the rectum it may produce a desire to defecate. The intra-abdominal pressure is raised by the simultaneous contraction of the abdominal and diaphragmatic muscles. Large peristaltic movements of the descending colon and sigmoid empty their contents into the rectum and a relaxation of the anal sphincters allows the material to be evacuated.

Chronic Constipation

Since the intestinal contents normally pass through the small intestines in from three to six hours and through the large intestines in twenty hours or thereabout, it is evident that appreciable delays in the total time of passage through the intestinal tract will be more readily produced by disturbances in the motility of the large intestine than by motility disturbances in the small bowel. Chronic constipation is the name given to the slow passage of material through the intestines and particularly through the large intestines. While an infrequent evacuation of feces is evidence of chronic constipation, the reverse is not the case. It is well known that certain patients may have a daily evacuation of feces and yet the colon may be filled with an accumulation of fecal material. Indeed, diarrhea may result from irritation of the colon by retained fecal material

or periods of constipation and diarrhea may alternate. In either case the primary disturbance may be a massing of fecal material in the large intestine.

Pathogenesis of Constipation

Lack of Normal Stimuli

The transportation of material through the intestinal canal is governed chiefly by the action of the intestinal contents upon the local nervous mechanism and muscle fibers of the surrounding intestinal wall. The stimuli which exert this action may be of a chemical or mechanical nature. Among the chemical substances that normally influence the movements are certain products of intestinal decomposition, such as carbon dioxid, marsh gas, skatol, etc. We know nothing of conditions in which a disturbed motility is due to a specific lack of any one of these chemical stimuli. On the other hand, we know that constipation is favored by any condition in which relatively small quantities of material pass into the large intestines. Where little is eaten on account of gastric or other disease, where there is an obstruction in the esophagus or at the pylorus, or where constant vomiting prevents the retention of what has been swallowed, constipation is common. During absolute starvation the bowels may not move for weeks. Highly digestible diets, containing little residue in the form of cellulose, etc., likewise tend to produce constipation. This occurs, for example, when patients are placed on the diets usually prescribed for ulcer of the stomach.

Lack of Residue from Undue Digestion.—Certain individuals may digest even the normal diet unusually well; and this, according to A. Schmidt, is a frequent cause of chronic constipation. The stools of such constipated individuals contain not only less water but less nitrogen, fat, carbohydrates, cellulose and bacteria (Strasburger) than do the stools of normal individuals. This abnormally good utilization of food is, according to Schmidt, a cause and not a result of the constipation, for when normal individuals have been made constipated by the use of opium, their absorption may be poorer than in the chronic constipation of this type. Constipation is frequently associated with gastric hyperacidity. It is well known that proteins are unusually well digested in the stomach of such patients, and that hyperacid gastric contents possibly cause an increased flow of bile and of pancreatic juice with a more perfect digestion and absorption in the intestines. It is evident, therefore, that under such conditions an unusually small residue may reach the large intestines and thus favor constipation.

Where constipation is due primarily to a lack of residue in the large intestines it may be relieved by taking food which contains increased quantities of non-digestible or non-absorbable material, such as agar, bran,

etc. These diets do in fact relieve certain cases of chronic constipation, mainly on account of their mechanical effect upon the large intestine.

Mechanical Causes

Mechanical obstructions may interfere with the passage of fecal material through the large intestines. Among the mechanical causes of constipation are peritoneal bands and adhesions which result from acute or chronic peritonitis. A constipation of this type may complicate or follow appendicitis, sigmoiditis, cholecystitis, duodenal and gastric ulcers, tuberculous peritonitis and inflammations of the female generative organs. Constipation may also be caused mechanically by the pressure of a floating kidney, a retroverted uterus, a displaced spleen or a malignant tumor. The pains which not infrequently accompany this type of constipation are due in part to the increased peristalsis proximal to the obstruction. Pain as well as fever may also be caused by inflammatory adhesions. In some of the conditions just noted, and particularly in those associated with inflammation, the constipation may be due not only to the mechanical obstruction but also to disturbances of the motor function of the large bowel.

Constipation in Enteroptosis.—It is well known that constipation frequently complicates enteroptosis, and the question has been raised whether this type may not be due to the mechanical effect of a low transverse colon which tends to produce kinks at the splenic and hepatic flexures. Although such kinking may occur it is not common. The constipation of such patients is usually due to other causes, and especially to atony of the muscle of the large colon. This is similar in character to the gastric atony frequently observed in these patients.

Functional Motor Disturbances

The motor disturbances of the large intestines in chronic constipation are usually due to alterations in function that do not depend upon any definite organic lesion. Following Fleiner, two main functional types of constipation have been distinguished. In the first, the so-called *atonic* type, the large intestines do not contract firmly upon their contents and there is presumably a diminished motility. In the second or *spastic* type, there is a spasm of certain portions of the large intestines which is believed to obstruct the forward movements of the intestinal contents. X-ray studies of patients suffering from chronic constipation have shown, however, that the actual conditions are usually more complex than such a classification would indicate. Atony or spasm, as judged from the size and configuration of the colon, is not necessarily accompanied by diminished motility, and spasm may affect one portion of the large intestine while other portions appear atonic.

Signs of Lack of Tone.—Diminution in tone is indicated by a large caliber and lack of haustral segmentation. This seems to be particularly common in the type of constipation which occurs as an hereditary affection, as well as in those forms which so frequently accompany senility, cachexia, fever, obesity and intestinal catarrh. It also occurs in certain nervous individuals and in mental diseases. Nervous reflexes may diminish the intestinal movements as has been shown by experiments on animals (compression of the testicles), and it seems probable that acute or chronic inflammations of the abdominal viscera may produce constipation through such reflexes.

Spastic Constipation.—Spastic constipation as described by the older writers occurs particularly in certain nervous individuals, in gynecological patients, in heavy smokers, etc. It is characterized by attacks of intestinal pain, tenesmus and tenderness on pressure over the colon. X-ray examinations have shown that spastic contractions of the large intestine are particularly common in the transverse and descending portions of the colon. The contents may be drawn out into narrow bands, the haustral segmentations may be unusually marked or the fecal material may be divided into numerous small balls. Evidences of spasm in the proximal colon are less frequent.

Neither the appearance of marked constrictions in the colon nor the appearance of lack of tone is necessarily accompanied by constipation. In fact, as we shall see, either one may accompany diarrhea. It seems certain, therefore, that the objective evidence of spasm or of atony cannot in itself be the sole cause of constipation.

Classification by Site of Stasis.—In view of the manifest difficulties in classifying constipation according to the degree of colonic contraction, it seems advantageous at the present time to adopt a classification based upon the main site of stasis. The commonest sites for such a stasis are the rectum and neighboring sigmoid, the ascending colon, and the lower ileum. Less commonly the transverse colon is the site of stasis.

(a) *Dyschezia*

The term dyschezia has been used by Hertz to designate those cases of constipation in which defecation itself is incomplete or delayed. The intestinal contents pass through the colon with normal, increased, or decreased rapidity; but, having reached the rectum or neighboring sigmoid, the fecal material remains here for an abnormally long time. In some cases it is only partly evacuated at defecation, so that the lower bowel, instead of being empty or nearly empty after defecation, constantly contains fecal material (cumulative constipation). Examination of the rectum usually discloses the nature of the condition. When, however, the stasis is confined to the sigmoid, diagnosis is more difficult. In these

cases the x-ray examination shows that fecal material remains in this portion of the intestine for an abnormally long time.

Two Main Causes.—According to Hertz there are two chief causes of dyschezia: (1) neglect to respond to the normal call to stool which leads to distention and atony of the lower bowel; and (2) a weakness of the voluntary muscles that assist defecation. Changes in the nervous mechanism of the lower bowel and mechanical obstructions in this region, either from without or from changes in the rectum itself, are also possible. In the treatment of dyschezia especial attention should be paid to the call for defecation, and enemata rather than cathartics are indicated.

(*b*) *Ascending Stasis*

This type of constipation is characterized by an unusually long delay of intestinal material in the ascending portion of the large intestines. Here material may remain for 24 to 48 hours or even longer. Once past the ascending colon the material may proceed in the normal manner.

Cause Uncertain.—The cause of such an abnormally long delay in the proximal portion of the colon is uncertain. It may be due to atony or increased antiperistalsis in this region, it may be due to some difficulty in passing the portion of the intestine beyond, owing to organic obstruction or spastic contractions, or, finally, it may be due to an absence of the large colonic peristalses which are believed by some to constitute the normal mode of transporting material across the transverse colon. It is evident, however, that even normally the ascending colon is the site of some stasis, for the intestinal contents always remain in this region for some time. In the ascending type of constipation this stasis is increased.

Increased Digestion and Absorption.—Such stasis in the ascending portion of the colon tends to increase digestion and absorption in this part of the intestines. The increased destruction of cellulose and the increased absorption of water and nutritive material allow less material than usual to proceed into the distal colon, and as a result the distal colon receives less stimulation than normal. It would appear that in these cases particularly the feces contain less nutritive material than normal.

In some cases of ascending stasis local symptoms are entirely absent. In others feelings of pressure, distention and dyspepsia may accompany the constipation. At times the symptoms resemble those of mild or chronic appendicitis, the pains being due to distention, dragging, or spastic contractions of the cecum and neighboring colon.

(*c*) *Transverse Stasis*

Less common than the ascending type of constipation is that in which the principal stasis occurs in the transverse colon. This seems to occur

particularly in patients with ptosis of the transverse colon. In some such cases the low position of the colon or its lack of tone seems responsible for the constipation; in others a kinking at the splenic flexure may be the cause of stasis.

(*d*) *Ileal Stasis*

In a certain number of patients with gastro-intestinal complaints, and particularly in those suffering from constipation, x-ray observations have shown that the terminal ileum does not empty its contents as promptly into the cecum as it should. The cause of this ileal stasis may be a mechanical obstruction in the terminal ileum produced by malignant disease, by adhesions, or by kinks. According to Case, ileal stasis is not ordinarily due to mechanical obstructions in the terminal ileum, but is usually due to functional changes in the activity of the ileocecal sphincter. Normally this sphincter prevents the regurgitation of the colonic contents into the terminal ileum. When enemata are given the material fills the colon but is prevented from entering the ileum. Functional changes in the activity of this sphincter may consist of spasm or incompetency. Apparently spasm of the sphincter causes ileal stasis in a certain number of cases and particularly when, as in appendicitis, there is a local inflammation in this region.

Incompetency of Ileocecal Valve.—According to Case, however, the most frequent cause of ileal stasis is an incompetency of the ileocecal valve. On giving enemata to patients suffering from various abdominal diseases, he noted that, in approximately one patient out of six, the material contained in the enema passed from the colon into the terminal ileum. In certain patients also the bismuth taken by mouth was observed to pass into the cecum and later to return into the ileum. Finally, an incompetency of the valve has been demonstrated in certain patients at operation. The great majority of patients who show objective evidence of ileocecal insufficiency suffer from chronic constipation and at times from other intestinal symptoms. The condition is frequently associated with disease of the proximal colon, and particularly with stasis in this region. That incompetency of the ileocecal valves should itself favor constipation is obvious, when we recall that this valve normally prevents the entrance of material into the ileum during the antiperistaltic movements that occur in the first part of the colon.

Symptoms of Constipation

Patients suffering from chronic constipation may complain of no symptoms, even though defecation occurs only at intervals of four days or more. Local pains may be due to intestinal spasm, distention, or irritation of the mucous membrane by the fecal material. The association of

chronic constipation with nervous symptoms is common but its exact cause is not clear. Such nervous manifestations are frequently attributed to the absorption of toxic material from the bowels. When we remember, however, that the feces in constipation usually show an usually good absorption of material, and that the number of bacteria present is usually less than normal, it would seem that in most cases there is even less than the usual opportunity for the formation of poisonous material in the intestines. Furthermore, patients with chronic constipation commonly experience an unusual sense of well-being immediately after a satisfactory evacuation of the bowels, at which time there can be no change in the amount of absorbed material in the body. From these facts, it would appear that the nervous symptoms so frequent in these patients are due in part to the mechanical effect of the retained material.

Nevertheless it must be admitted that the possibility of some toxic absorption in chronic constipation and in other intestinal disturbances is not easily disproved. The conditions for such absorptions are particularly favorable when, owing to ileocecal incompetency, colonic material is returned into the small intestine. This question will be discussed more fully in the paragraphs on intestinal auto-intoxication.

Diarrhea

Diarrhea, like constipation, depends primarily upon disturbances in the motility of the large intestines. Motor changes in the small intestines may or may not be present. Increased motor activities in the small intestines, such as occur in "peristaltic unrest," with its splashing and gurgling sounds and violent peristalsis visible through the abdominal walls, are not necessarily accompanied by diarrhea.

Pathogenesis of Diarrhea

Excess of Stimuli

Just as constipation may be due to a lack of normal stimuli owing to the small bulk or chemical nature of the contents of the large intestines, so diarrhea may be due to the excessive stimulating properties of the colonic contents. The diarrhea which follows certain indiscretions in diet (green fruit) is of this character, as is also the diarrhea provoked by most purges. In certain cases of pancreatic disease the reduced absorption leads to copious and more numerous bowel movements, which may take on a diarrheal character.

Gastric Achlorhydria.—Chronic or intermittent diarrheas may accompany gastric achlorhydria, particularly when this is associated with insufficient chewing of the food (bad teeth). Although diarrhea occurs in only a moderate proportion of patients showing achlorhydria, this is one of the

commoner types of chronic diarrhea in temperate climates. In such cases the diarrhea is due in part to the mechanical irritation of the undigested food that leaves the stomach. In part it is due to unusual bacterial activities in the intestines. Owing to the achlorhydria and to the hypermotility of the stomach so frequently present, bacteria taken in the food gain ready access to the intestines, while the increased residue of undigested food in the intestines furnishes an unusual opportunity for their development. Peristalsis is stimulated by the excessive or abnormal decomposition of the food in the intestines and by the action of the bacteria themselves. The use of finely divided food and the administration of hydrochloric acid after meals may check the diarrhea in such patients.

Unusual bacteria which have gained entrance to the intestine may also cause diarrhea, as happens, for example, in Asiatic cholera, bacillary dysentery, paratyphoid infections, etc. For the most part these diarrheas are associated with organic changes in the large intestines.

Increased Irritability of the Intestines

No sharp line of demarcation exists between the diarrheas that are due to abnormal stimulation of the intestines and those that are due to changes in intestinal irritability; for infecting organisms and decomposing food not only stimulate the normal intestines, but also damage the intestinal wall, and thus render it abnormally irritable. Inflammation of the walls of the large intestine, with or without ulceration, is usually accompanied by diarrhea. In some cases, however, catarrhal changes in the large intestines are associated with constipation.

That nervous influences may play a part in the etiology of diarrhea is evident from the well-known fact that nervous strain may cause a desire to defecate; and it seems not unlikely that diarrheas of purely nervous origin do occasionally occur. On the other hand, it is certain that many diarrheas, ordinarily regarded as nervous, are due to organic changes in the large intestines, or to unusual stimuli which these receive by reason of the character of their contents. With more careful study many cases of supposed nervous diarrhea are found to belong more properly to the class of functional diarrheas due to gastric achlorhydria, intestinal fermentation, or intestinal putrefaction.

Motility Changes in Diarrhea

Although relatively few studies have been made with the x-ray of the intestinal activities during diarrhea, it is evident from these, as well as from studies of the action of cathartics, that diarrhea may be associated with a great diversity of changes in the appearance of the bowels. The caliber of the large intestines, as well as the prominence and activity of their haustral sacculations, varies. Increased tone and increased haustral ac-

tivity are present after certain vegetable cathartics, particularly senna and aloes, and similar changes in certain patients with diarrhea, have led Stierlin to bring these latter together under the term "spastic diarrheas." These spastic diarrheas, which are characterized by the increased tone of the large intestines, seem to belong more particularly to the class of functional or nervous diarrheas. Other cathartics, notably castor oil, are associated with diminished prominence and diminished activity of the haustral segmentations. A similar lack of haustral segmentation is present in certain patients with chronic diarrhea, particularly when the latter is due to ulcerative colitis. In the region of the ulcerations, however, the motility is usually increased, so that in these regions no bismuth is ordinarily seen.

Increased Peristaltic Movements.—It is evident from these observations that the degree of tonus, as judged from the caliber of the large intestines and the prominence and activity of the haustral segmentations, bears no definite relation to the rapidity of passage through the large intestine. Spastic constipation and spastic diarrheas give similar pictures, while atony may be associated with either constipation or diarrhea. Diarrhea depends, therefore, not upon changes in the tone of the large intestines, but upon other disturbances of their motor activities. An increase in the peristaltic movements, and particularly in the large peristaltic movements described by Holzknecht, seems the most probable motor change in diarrhea.

Intestinal Obstruction

The effects of intestinal obstruction vary greatly. In some cases the disease is rapidly fatal, while in others the obstructive symptoms may be present for weeks or months before the patient's condition becomes alarming. Naturally the severity of the symptoms is determined largely by the degree of obstruction. The more complete the obstruction the more rapid will be the course of the disease. A number of other factors, however, influence the clinical picture. Obstructions in the upper part of the small intestines generally pursue a more acute course than those in the lower intestines. Furthermore, obstructions which are associated with interferences in the blood supply to the affected bowel are relatively serious.

Motor Disturbances

The immediate effect of an intestinal obstruction is a delay in the passage of intestinal contents past the point of obstruction. Material accumulates on its proximal side, and this accumulation incites the affected intestine to increased motor activity, partly by mechanical distention, and partly also by the chemical stimulus of the products of digestion or decomposition. Rhythmic segmentation may be increased. Particularly characteristic, however, are the unusual number of deep peristaltic waves which sweep over the distended intestine up to the point of obstruction. These

have been observed by the x-ray both in animals and man. Inspection of the external abdominal wall may also show distended loops of intestine firmly contracted on their contents (intestinal stiffening) with visible peristalsis in the distended loops. These contractions of the distended intestine give rise to cramplike pains. Such increased motor activity tends to force intestinal contents past the point of obstruction, and it may, therefore, be regarded as a compensatory phenomenon.

Vomiting.—Vomiting is an early and fairly constant symptom in intestinal obstruction. In the earlier stages the vomitus consists of gastric or duodenal contents, and it is comparable to the vomiting of any serious abdominal irritation. Later, however, the vomitus often contains fecal material derived from the intestines. This is due in part to the collection of large quantities of fluid in the intestinal coils above the obstruction, and is thus simply an overflow from the filled intestines. The material may also be carried back from the obstruction by antiperistaltic contractions. These have been observed in experimental obstructions in animals, and there is reason to believe that they also occur in man, being similar to the antiperistaltic movements seen in the stomach in cases of pyloric obstruction. They are particularly marked in obstructions localized in the colon.

Distention and Diminished Movement.—As a result of the increased pressure to which the coils of intestines lying proximal to the obstruction are subjected, they tend to become dilated, and eventually they may show a diminution of movements. Gas and also liquids are present in the dilated intestines, and a definite collection of gas may be observed in the most distended region. The movements of the intestines that lie distal to the obstruction are usually diminished, owing to lack of contents or to toxic or infectious causes. In some cases they become atonic and gas accumulates in them also, giving rise to general abdominal distention.

General Symptoms

Sooner or later during the course of an intestinal obstruction the patient develops symptoms of a general toxic character. The pulse and respirations become rapid, the blood pressure falls, there is cyanosis with or without clammy skin, and great prostration appears. The mental condition varies from a noisy delirium to a more or less marked stupor which may terminate in unconsciousness. Albuminuria is common. These symptoms have been attributed to various causes. Systemic bacterial infection, general peritonitis, nervous shock, loss of liquids from constant vomiting, and intoxication produced by absorption of toxic material from the affected intestine have each been held responsible for the general symptoms of intestinal obstruction. Each may play a part in particular instances, but their relative importance has been variously estimated.

High Intestinal Obstruction.—Particular attention has been paid to

the rapidly fatal results which follow complete obstruction in the duodenum or upper portion of the jejunum. This type of obstruction has been studied experimentally in dogs by Draper, Hartwell, Whipple and their coworkers, and it has been shown that in these cases systemic infection can be excluded as a cause of the early death. Hartwell and his associates have emphasized the importance of losses of liquid in these high obstructions. When the large quantities of vomited liquids were replaced by subcutaneous injections and damage to the mucosa was carefully avoided, their dogs, instead of dying invariably in ten days or less, were alive and in good condition at the end of three weeks, and apparently would have succumbed only to starvation if the experiment had been continued. Whipple and his associates produced a closed loop of duodenum just below the point of entrance of the pancreatic and bile ducts, and then established an anastomosis between the stomach and the remaining intestines, so that food material as well as bile, pancreatic juice, and gastric secretion could pass freely into the lower intestines. Dogs so treated died in from 36-72 hours, evidently on account of an absorption of toxic material from the closed loop of intestines. This toxic material is derived from the intestinal mucosa itself, and probably depends upon changes in the mucosa. The toxic material, according to Whipple, belongs to the class of proteoses. Anything which interferes with the local circulation (strangulation) increases both the production and absorption of toxic substances. These studies have shown, therefore, that the rapidly fatal results of high intestinal obstruction are independent of bacterial infection, and depend partly upon water losses from vomiting, and partly upon the absorption of toxic material which may be derived from the damaged mucous membrane of the duodenum or upper jejunum.

Obstruction at Lower Levels.—Obstruction at lower levels of the intestines is less rapidly fatal than that in or near the duodenum. This is due in part to the fact that the vomiting of liquid is less profuse in such cases. The large amount of fluid poured out by the stomach, pancreas and liver, instead of being lost to the body by vomiting, can be in part resorbed by the longer length of intestines that intervenes before the obstruction is reached. Furthermore, the lower intestines do not give rise to such virulent toxic material as does the duodenum and the adjacent jejunum. Closed loops of the large intestines produce such slight toxic effects that dogs with such loops may remain alive for months. In lower intestinal obstruction, therefore, circulatory changes in the intestinal walls, and general or localized invasions of bacteria, play a relatively important rôle in producing the symptoms of obstruction.

Intestinal Paresis

But little is known concerning a diminution in the motor activities of the intestines other than that which leads to chronic constipation.

Yet it seems certain that intestinal paresis plays an important part in various pathological conditions.

After Abdominal Operations.—Paralysis of the intestines occasionally develops after operations, and particularly after abdominal operations, even though there is no general peritonitis. The various factors governing this type of intestinal paresis have been studied experimentally in the cat by Cannon and Murphy. These authors found that simple etherization was followed by a delayed passage of food from the stomach. Exposure or cooling of the intestines produced no further deleterious effect upon the intestinal activities. When, however, the intestines were roughly handled at the time of the operation, this was followed by a very definite delay in the emptying of the stomach and by a slow passage of material through the small intestines. Further experiments showed that these changes in the motor activities of the gastro-intestinal canal were not influenced by cutting the extrinsic nerves to the canal. They were, therefore, due to changes in the local motor mechanisms in the intestines themselves. The intestinal movements may also be inhibited reflexly by traumata to the testicles or by the operation of opening the abdominal wall, an inhibition which does not occur if the splanchnic nerves are cut.

In Infectious Diseases.—In various infections, such as pneumonia and typhoid fever, marked distention of the intestines not infrequently becomes a serious factor in the disease. This may be associated either with constipation or diarrhea. It seems probable that such conditions are comparable to the distention which occasionally appears after operation, a supposition which is supported by Cannon's observation that in the distemper of dogs the food may lie all day in the stomach or intestines without the slightest indication of being acted upon by peristalsis. In general peritonitis the serious paralysis of the intestines with lack of motion and gaseous distention is due in part to this action of infections in general, but the unusually serious character of the intestinal paresis in this condition indicates that it is due chiefly to the deleterious effect of the local changes.

Intestinal Pain

The sensibility of the anal canal is very similar to that of the neighboring skin. Except for this region, however, the sensibility of the intestines is similar to that of the stomach. Hertz has shown that the mucous membrane of the colon is insensitive to tactile stimuli, and little if at all sensitive to thermal stimuli. On the other hand, it is sensitive to artificial distention. If this be done slowly and be not too excessive, the individual experiences a sensation of fullness similar to that felt when there is gas in the colon. If, however, the colon is rapidly and forcibly distended, a sensation of pain is produced owing to the tension on the muscular fibers.

Abnormal Motor Activity.—The intestinal pains that are observed clinically are probably always due either to abnormal motor activities

of the intestines or to peritoneal disease. Ulcerations such as those of typhoid fever ordinarily produce no pain. Nor are the usual forms of peristalsis painful. In intestinal obstruction the severe cramplike pains can sometimes be seen to coincide with firm tetanic contractions of the intestine that lies proximal to the stenosis. As the "intestinal stiffening" lessens, the pain subsides. The pain, in this instance, is evidently due to the unusually firm contraction of the intestine upon contents which are not permitted to pass the point of obstruction. Other forms of intestinal cramps and pains, such as those which occur in lead colic, are probably of similar origin, except that instead of an organic obstruction there is here a spasm which opposes the propulsion of material along the intestines by a peristaltic wave. The increased tension of the intestinal wall gives rise to intestinal pain, just as the increased tension of the stomach may give rise to gastric pain.

Local Peritonitis and Adhesions.—Pains may also be caused by local peritonitis and adhesions, and particularly when these involve the parietal peritoneum. According to Hertz, the pain that is produced in the movable portion of the intestines is usually referred by the patient to the region of the umbilicus, whereas the pain which is produced in the more fixed portions of the intestine is referred to the general region of the abdomen from which the pain comes. When pain is caused by a localized peritonitis, it is likewise usually referred to the region of the disease. Diseases of the intestines may also give rise to pain that is referred to the distribution of the cutaneous nerves which enter the same region of the cord as those coming from the intestines, being similar to the referred pains of angina pectoris. In appendicitis, for example, Hertz distinguishes the early pain that is localized in the umbilicus, the pain of an associated peritonitis that is localized in the region of the abdomen affected, and the referred nervous pain in the right iliac fossa. When the appendix occupies some unusual position in the peritoneal cavity the referred nervous pains may be in the right iliac fossa, while the pains due to local peritonitis may be near the seat of the disease.

Intestinal Auto-intoxication

No topic in medicine has been the subject of more speculation than intestinal auto-intoxication. According to some, the greatest variety of complaints and diseases originate from this cause; according to others, no positive evidence exists that intestinal auto-intoxication is a cause of disease.

Conditions to be Excluded.—In order to restrict the discussion, it becomes necessary, first of all, to exclude a number of conditions which are not usually classed among intestinal auto-intoxications in the narrower sense. Intestinal infections, for example, with penetration of microörganism into the mucous membrane, cannot properly be classed as intoxica-

tions. We now know that many epidemics of food poisoning are due, not to poisons preformed in the food, but to an infection with some microörganism contained therein. Bacteria of the paratyphoid group are often responsible for such food infections. In the second place, one must exclude from auto-intoxication all those toxic conditions which are caused by the introduction of preformed poisonous substances into the alimentary canal. Poisonings with the ordinary mineral or alkaloidal poisons, with mushrooms, ergot, as well as poisonings with preformed bacterial toxins that are taken as such into the alimentary tract, are to be excluded from intestinal auto-intoxications in the narrower sense. Finally, one may, for the sake of simplicity, exclude from consideration the diseases which are due to the absorption of unchanged proteins by individuals who are sensitive to these proteins. Idiosyncrasies to eggs, to shellfish, to buckwheat, and to other protein substances are now believed to be due to the passage of their proteins in an unchanged condition through the wall of the alimentary canal, and similar toxic symptoms can usually be produced when the same proteins are introduced directly into the bodies of susceptible individuals by other routes. The most common symptoms produced by this type of intoxication are urticarial or other rashes, asthmatic symptoms, etc., which will be discussed in the paragraphs on anaphylaxis. These conditions, though classed with the intoxications that enter the body through the intestinal wall, are not caused by toxic substances in the ordinary sense of the word, nor do they depend upon alterations of the intestinal contents. They are due rather to an abnormal sensitiveness on the part of the patient.

Definition of Term.—In the more restricted sense, we understand by intestinal auto-intoxication the pathological effects produced by some poison or poisons that have been formed in the intestines. Such poisons may arise from a decomposition of the food in the intestines; they may be products of bacterial growth in the intestines, or they may be produced in or by the mucous membrane itself.

Evidence Largely Clinical.—The evidence that intestinal auto-intoxications actually exist in man is based largely upon clinical rather than upon experimental evidence, and upon the knowledge that poisonous materials may be formed in the intestines rather than upon the demonstration that a particular substance has been the cause of symptoms in a particular case or group of cases. Among the minor symptoms commonly attributed to intestinal toxemia are headache, lassitude, loss of appetite, coated tongue, muscular and mental fatigue, irritability; in fact, a group of neurasthenic symptoms. A number of skin lesions, particularly those of an urticarial or erythematous character, may undoubtedly arise from the absorption of substances from the alimentary tract. It has just been pointed out, however, that these symptoms are often due to an individual hypersensitiveness to certain proteins rather than to the formation of peculiar toxic substances

in the intestines. Among the more serious conditions often attributed to intestinal auto-intoxication are pernicious anemia, arteriosclerosis, chronic nephritis, etc. The casual relation between these latter conditions, while suggestive in certain ways, still awaits demonstration.

Neurasthenic Symptoms.—In regard to the symptoms of a neurasthenic character, it is difficult to form a correct judgment. We have pointed out that the observation, so frequently made, that constipated patients often feel immensely relieved so soon as the bowels move, cannot be interpreted in favor of the view that their symptoms are due to the absorption of toxic material from the intestines. Such an immediate relief is due either to a psychic effect or to a lessening of the mechanical distention of the colon. Colonic distention produces a sense of fullness even in normal individuals. The general improvement in the health of constipated subjects, that often seems to follow regulation of the bowels by medical and surgical means, is difficult to interpret. In some patients constipation has become an obsession, and relief from this symptom is the best form of psychic therapy. Nevertheless, even though one take into consideration these various factors, one frequently gets the impression that a low grade poisoning occurs in certain patients with intestinal disturbances. How often this occurs and what is its immediate cause are problems for the future.

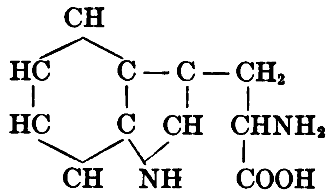
Three Possible Sources of Auto-intoxication.—There are three possible origins for toxic material in the intestines. The first is from the mucous membrane itself. In the case of experimental obstruction in the duodenum and upper jejunum the intoxication seems to arise mainly from this source (page 193). The lower small bowel may give rise to similar toxic substances, though in smaller amounts. Apparently none arise from the mucous membrane of the colon.

In the second place, intestinal auto-intoxication may be produced by the bacteria that inhabit the intestinal canal under normal or pathological conditions. So far as we know, however, soluble toxins are not produced by the normal bacterial flora residing in the intestines. That they may arise from this source is possible but it is not proved. Adami has held, however, that low grade infections from the intestinal tract are not infrequent, and that such subinfections may possibly be responsible for some of the symptoms ordinarily attributed to intestinal toxemias.

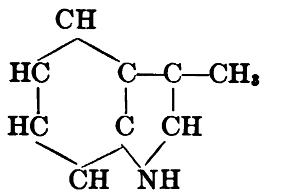
The third source of intestinal auto-intoxication are the decomposition products that arise from the food and other material in the intestines. During the cleavage of these substances by the digestive ferments, as well as by bacteria, it is conceivable that toxic products may be formed and later absorbed. Particularly in the case of the proteins are such formations possible. The attention of earlier investigators was directed particularly toward the formation of indol, skatol, phenol and cresol in the intestines.

Indol and Indoxyl.—Indol and skatol are formed by the bacterial

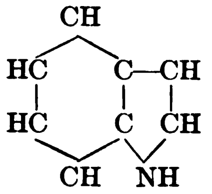
decomposition of tryptophan, a protein-building stone. After absorption indol is oxidized to indoxyl, and this unites with sulphuric acid in the body and is excreted as an ethereal sulphate.



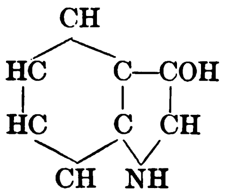
Tryptophan



Skatol



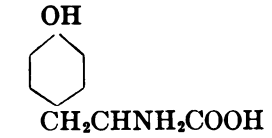
Indol



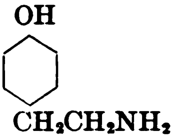
Indoxyl

Indican or indoxyl sulphate may be estimated in the urine by its color reactions. The amount excreted in the urine depends not only on bacterial decomposition in the intestines, but also upon the available tryptophan and the amount of indol absorbed by the intestinal wall. When the small intestines are experimentally obstructed there is usually a marked increase of indican in the urine; after obstruction of the large intestines no such marked increase occurs. In chronic constipation the amount of indican in the urine may be normal, diminished, or increased. It is certain that a marked stasis of material in the large intestine may cause no unusual quantities of indican to appear in the urine. On the other hand, Kellogg has recently pointed out that patients with ileal stasis usually show unusual quantities of indican in the urine. Stasis in the small intestines is, therefore, one important cause of a pathological indicanuria. The absorption of indol from the intestines does not necessarily produce symptoms. By oxidizing indol to indoxyl, and by combining the latter with sulphuric acid, the body protects itself against any poisonous action. Few if any symptoms are produced by the administration of indol, and the symptoms of intestinal toxemia do not run parallel to the amount of indican found in the urine. At best, therefore, the appearance of unusual quantities of indican in the urine indicates some unusual bacterial decomposition in the intestines, and particularly in the small intestines.

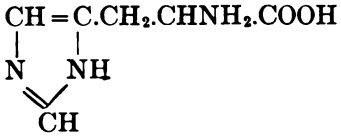
Toxic Amins.—Renewed interest in the problem of intestinal toxemia has followed the demonstration that certain of the amino acids derived from the breaking down of proteins are able to furnish exceedingly toxic amins by the removal of one carbon dioxid complex. The reaction is shown in the following formulae:



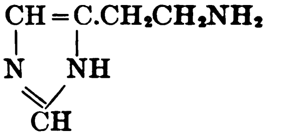
Tyrosin



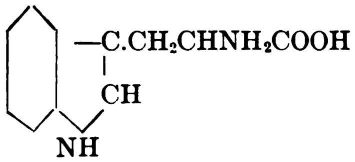
Hydroxyphenylethylamin
(very poisonous)



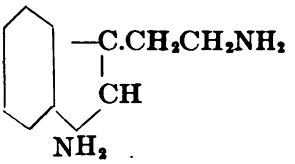
Histidin



Beta-iminazolylethylamin
(very poisonous)



Tryptophan



Indolethylamin (poisonous)

These amins are powerful poisons. If they were formed in excessive quantity in the intestines and were not immediately broken down into simpler and less toxic substances, they might be absorbed and give rise to serious symptoms. Certain of them have been produced by the activity of bacteria derived from the feces, and some have been found under special conditions in the intestines. According to Harvey, also, the continued injection of these substances may produce serious chronic disease in animals. As yet, however, we know practically nothing of their relation to clinical conditions.

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Chapter III

The Metabolism

The Energy Metabolism

The products of digestion, absorbed from the gastro-intestinal canal, undergo various transformations in the body. Some are broken down almost immediately into simpler compounds which are then eliminated from the body by the excretory organs, some are stored either unchanged or after modification and are used later as needed, while still others serve to build up the complex living protoplasm of the tissues and are ultimately disintegrated into waste material. These chemical transformations within the body constitute its metabolism.

Methods of Study

In studying metabolism, one may follow an individual food material from the time of its absorption until it is finally converted into waste products. In this way, one may speak of a protein metabolism, a fat metabolism, etc. Certain disturbances in these separate metabolisms will be considered partly in this and partly in the following chapters. On the other hand, metabolism may be considered collectively from the standpoint of energy transformations. The body is a combustion apparatus in which various materials derived from the food are hydrolyzed, oxidized, and otherwise altered by means of special ferments, until they finally liberate energy which leaves the body mainly in the form of heat. Thus the total metabolism in the body may be expressed in terms of energy, and the heat unit or calorie is commonly used for this purpose.

Direct Calorimetry.—The total metabolism may be determined directly by placing the individual in a suitable calorimeter and measuring the heat given off from the body through conduction, radiation and evaporation; at the same time making allowances for any change in the temperature of the body itself. This is the method of direct calorimetry.

Indirect Calorimetry.—The energy liberated in the body may also be calculated if we know how many grams of fat, of carbohydrate, and of

protein are consumed in a given time, for each gram in burning liberates a definite and known amount of heat. When the ordinary foodstuffs are oxidized to the same end products as are formed in the body, each gram yields the following number of calories:

	Calories
Glucose	3.8
Cane Sugar	4.0
Starch	4.1
Fat	9.3
Protein	4.1

This method of determining the total metabolism is called indirect calorimetry.

Respiratory Quotient.—In order to determine the total metabolism by this method, it is necessary to estimate the amount and kind of material consumed in the body. This is done by a study of the waste products eliminated. The nitrogenous waste in the urine furnishes an index of the rate of protein metabolism. The absorption of oxygen and the elimination of carbon dioxid through the lungs furnish a measure of the metabolism of carbohydrates, fats, and the non-nitrogenous portion of the proteins, for all these are burned to carbon dioxid and water, and the former leaves the body in the expired air. The separate amounts of fats and carbohydrates burned are estimated by determining the ratio between the volume of carbon dioxid given off from and the volume of oxygen absorbed by the lungs. This ratio is called the respiratory quotient.

$$\text{Respiratory quotient} = \frac{\text{Vol. } CO_2}{\text{Vol. } O_2}.$$

When carbohydrates alone are burned, the reaction may be represented by the following formula:

$$\underset{\text{Glucose}}{C_6H_{12}O_6} + \underset{\text{Oxygen}}{6\ O_2} = \underset{\text{Water}}{6\ H_2O} + \underset{\text{Carbon Dioxid.}}{6\ CO_2}$$

The respiratory quotient here is equal to 1.0. When fats alone are burned the completed reaction may be expressed by the formula:

$$\underset{\text{Palmitin}}{2\ C_{53}H_{98}O_6} + \underset{\text{Oxygen}}{145\ O_2} = \underset{\text{Water}}{98H_2O} + \underset{\text{Carbon Dioxid.}}{102\ CO_2}$$

The respiratory quotient here is equal to 102 divided by 145 or approximately 0.7. Knowing the respiratory quotient, therefore, it is possible, after allowing for the effects of protein metabolism, to estimate the relative amounts of fats and carbohydrates that have been burned in a given time. A quotient of 0.85, for example, if derived wholly from a

combustion of fats and carbohydrates, would represent a combustion of such quantities that equal amounts of carbon dioxid were derived from each.

Retention of Heat and Waste.—Direct as well as indirect calorimetric determinations must take into consideration the fact that heat as well as waste products may be temporarily retained in the body. In direct calorimetry, for example, the temperature of the body must be controlled, for a rise of body temperature will indicate that the heat formed in the body has not all been given off to the calorimeter. Similarly, a retention of nitrogen or of carbon dioxid in the body will interfere with the indirect calculations. It is obvious that with a long period of observation the errors from these sources will lessen, for in the long run the amount of heat formed is equal to the amount eliminated, and the same is true of the waste products.

The results obtained by the methods of direct and indirect calorimetry agree very closely and within the limits of experimental error, thus proving that, when various food materials are burned within the bodies of animals or of man, they liberate the same amounts of heat as when they are burned to the same waste products outside the body.

The Rate of Metabolism

Physiological Variations in a Given Individual

Determinations of the rate at which heat is formed in the body show that this is subject to very considerable variations even in a given individual. Of the factors that influence the rate of metabolism in a normal man the most important are: first, muscular exercise and possibly other physiological activities of the waking life; and, second, the ingestion of food.

(a) Muscular Exercises

Muscular exercise influences the rate of metabolism to a greater degree than any other individual factor. The following table, taken from the observations of Benedict and Carpenter, illustrates the effect of exercise:

Effect of Muscular Activity on Heat Production

Kind of Activity	Heat Produced in One Hour in Calories
Man at rest, sleeping	71
Man at rest, awake and sitting	97
Man at rest, standing	114
Man at very severe exercise	654

It is evident, from the difference of about 17 per cent between the sitting and standing metabolism, that even slight muscular exercise increases the rate of metabolism to an appreciable extent. It is evident also, from the maximum figure given in this table, that very violent exercise may increase the rate of metabolism to eight or nine times its minimum rate. The maximum here recorded was observed in a trained athlete during bicycle riding and was probably about the greatest metabolism of which such a man is capable. Lesser grades of exercise are difficult to define in exact terms. The effect of walking was studied by Zuntz and his associates. They found that walking on the level at a moderate pace increased the rate of metabolism up to about three times the resting rate, walking rapidly on a level increased it to about five times the resting, while walking rapidly up a steep incline might increase it to almost nine times the resting value.

Minor Muscular Activities.—It is evident from these observations that even minor grades of muscular activity exercise a marked influence upon the rate of metabolism. In all metabolic studies, therefore, the amount of muscular movement must be controlled with the greatest care.

According to Benedict, there is also a distinct difference between the metabolism of an individual who is sleeping and the metabolism of this same individual when he is lying quietly in bed with no evident muscular tension and with no external movements, the difference being in the neighborhood of 13 per cent. Benedict has found, furthermore, that the metabolism in the afternoon is, as a rule, somewhat higher than it is in the morning. It seems probable, therefore, that the physiological activities of the waking day increase the body metabolism to some extent, even though they be associated with no demonstrable change in muscular activity.

Chilliness and Muscular Tone.—When a person or an animal is exposed to cold, the resulting chilliness may cause an evident increase in the muscular tone. If the chilliness is marked, it causes the involuntary muscular movements that we recognize as shivering. Such muscular activities and particularly shivering cause a definite increase in the rate of metabolism. In the dog, exposure to cold seems to increase the rate of metabolism, quite apart from the occurrence of obvious muscular movements. In man, however, this does not occur and apparently no increase in metabolism follows exposure to cold, provided there is muscular relaxation and muscular quiet.

(b) The Effect of Food

It is common knowledge that when a large meal is eaten during warm weather, the individual feels warmer and perspires more freely. During cold weather a large meal increases the resistance to cold. Metabolic studies have shown that there is a greater liberation of heat in the body

after the ingestion of food and that this may last for twelve hours or more. The amount of heat set free varies with the kind of food taken, protein increasing the metabolism to a greater extent than either fat or carbohydrates. Indeed, a very large meal of meat given to a dog may double its fasting metabolism. According to Rubner, a dog kept in surroundings of 33° C. and given the quantity of food that will just supply its fasting energy requirements shows the following increases beyond the normal fasting metabolism with the different kinds of food taken:

Protein	30.9	per cent
Fat	12.7	" "
Cane sugar	5.8	" "

In man, according to Du Bois, the ingestion of 200 grams of dextrose, or the ingestion of an amount of casein equivalent to 10.5 grams of nitrogen, increases the fasting metabolism by about 12 per cent.

Cause of Increased Metabolism After Food.—The cause of this liberation of heat after eating has been a subject of much discussion. It now seems established that no appreciable part of the increase is due to an increase in the motor and secretory activities of the digestive organs. Neither a saline cathartic nor a bulky and indigestible food, such as agar, causes a definite increase in metabolism. Furthermore, when the pancreatic juice is excluded from the intestines of dogs the increased amount of undigested food in the intestines causes no marked increase in metabolism. Finally, bouillon which stimulates the secretion of gastric juice is without effect upon the general metabolism. It is evident, therefore, that the increase in metabolism observed after eating must depend upon some effect produced by the products of digestion after they have been absorbed from the gastro-intestinal canal.

Rubner believed that the increased heat liberated after the ingestion of food was derived mainly from a series of transformations in the material absorbed, and that this had nothing to do with the fundamental activities of the living tissue. According to Lusk, however, the increased heat production is due, as Voit originally believed, to an increase in the metabolic activities of the cells. Lusk believes that an influx of fat or or carbohydrates enables the cells to oxidize more rapidly, because of the increased mass of food material that surrounds them. The unusually marked effect of protein, however, is attributed by Lusk to the action of certain decomposition products of proteins, especially those derived from alanin and glycocoll. These directly stimulate the living protoplasm to increased activity, without themselves necessarily taking part in the increased oxidative processes. A somewhat similar action is attributed by Benedict and Joslin to the acids present in the body in diabetic acidosis.

The Basal Metabolism

It is obvious that since the rate of metabolism is subject to marked physiological fluctuations, any determination that will be useful for purposes of comparison must eliminate, so far as possible, the effects of exercise and of food. For this reason it has become customary to determine the energy metabolism: (1) when the individual is fasting in the morning, from fourteen to eighteen hours after the last meal; and (2) with the individual in as complete muscular repose as possible. The energy metabolism under these conditions is spoken of as the basal metabolism. This is not the lowest possible metabolism, for Benedict has shown that the metabolism sinks to a still lower level during sleep. It furnishes, however, a convenient basis of comparison for different individuals and for the same individual on different occasions.

The Normal Basal Metabolism

When the basal metabolisms of different individuals are compared, it is found that these show considerable differences. In a general way, the basal metabolism increases with the weight of the subject, and for this reason the rate of metabolism per unit of body weight has been used as a basis of comparison. According to Benedict's recent compilation, the average basal metabolism of normal adults is about 25 calories per kilo of body weight per day. There is, however, a considerable variation on either side of this average, the limits in Benedict's determinations being from 18.1 to 32.3 calories. Lighter individuals, though showing a smaller total metabolism than heavier ones, usually have a greater metabolism per unit of body weight. Similarly, tall individuals usually have a greater metabolism than short individuals of the same weight. For this reason it has been proposed to compare the rate of metabolism with the area of the body surface. Gephart and Du Bois, for example, adopted a basal metabolism of 34.7 calories per square meter of body surface per hour as the standard of heat production for normal men between the ages of 20 and 50 years. Benedict has pointed out, however, that it is difficult to establish a satisfactory basis of comparison even with reference to the body surface. Thus athletes possess a somewhat higher rate of metabolism than do less active men of the same weight and height, apparently because they have a greater amount of active protoplasm; and men show a somewhat higher rate than women for the same reason. Furthermore, young individuals have a more rapid metabolism than elderly individuals. It would seem that the rate of metabolism is determined; (1) by the amount of living protoplasmic tissue; and (2) by the activity of this tissue. The latter may be stimulated by substances that are formed within the body.

Standards of Comparison.—It is evident, however, that comparisons between normal and pathological individuals require the adoption of some more tangible standard than the mass of active protoplasmic tissue. Perhaps the most satisfactory comparisons are made by comparing the metabolism of a given pathological individual with those of a group of normal individuals of the same age, weight and height. Next in order of value are comparisons based on the heat production per unit of body surface. According to Du Bois, a deviation of 10 per cent from his normal is probably pathological and a deviation of 15 per cent is definitely so. It is necessary to remember, however, that inactive material, such as fat or collections of fluid or edema, will add to the weight, and to a lesser extent to the surface, without increasing the rate of metabolism to a corresponding degree.

Pathological Variations in Basal Metabolism

A *pathological increase* in the basal metabolism is caused by certain forms of thyroid disease (hyperthyroidism). Magnus-Levy and others have shown that in exophthalmic goiter the basal metabolism may be fifty to ninety per cent above the normal. An even greater increase was observed by Cannon in cats suffering from experimental hyperthyroidism, which had been produced by grafting the phrenic on the cervical sympathetic nerve. When thyroid extract is administered to normal individuals the effect upon the metabolism seems to vary in different experiments. Apparently certain individuals are not highly susceptible to its action. Failures to increase the metabolism may also be due to an inactive preparation, or to failure to give the preparation for a sufficiently long time or in sufficiently large doses. In certain instances, however, thyroid substance has produced well-marked increases in metabolism. This has been particularly true when it has been given for therapeutic purposes to obese individuals, and to those suffering from myxedema or other forms of hypothyroidism (Fig. 62).

In fever the basal metabolism is usually increased by from 20 to 50 per cent. In leukemia, according to Grafe, it is increased from 25 to 100 per cent apparently on account of the excessive metabolism of the blood cells. Increases have been also described in diabetic acidosis, in phosphorus poisoning, in phlorhizin poisoning, in severe anemias, and at high altitudes.

Reduced Basal Metabolism.—The basal metabolism is markedly reduced in conditions of diminished thyroid activity (myxedema, cretinism), being in some cases from 48 to 60 per cent of the normal. The administration of thyroid substance to such patients increases their metabolism to or above the normal. Grafe has also described a reduction of metabolism in psychopathic patients suffering from stupor. In the latter stage of prolonged starvation the rate of metabolism is diminished.

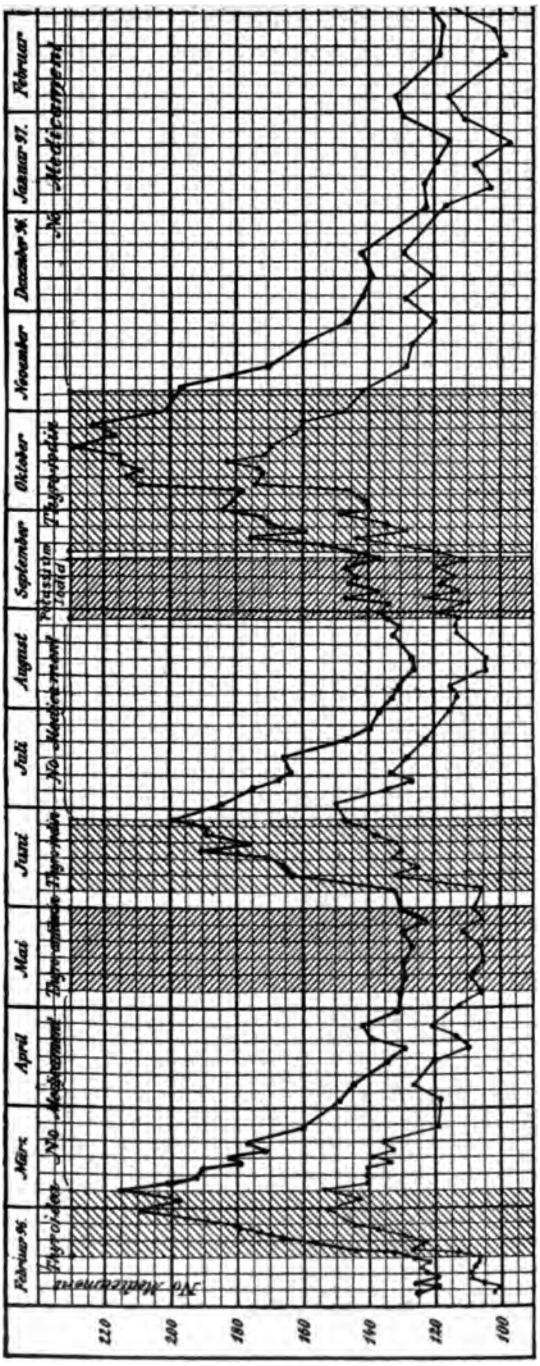


Fig. 62.—The Effect of Thyroid Medication on the Gaseous Metabolism of a Sporadic Cretin. Upper Curve Oxygen Consumption and Lower Curve Carbon Dioxid Elimination in c.c. per Minute. Note that Thyro-antitoxin Produced No Effect and Potassium Iodid But Slight Effect. Thyroid Preparations, on the Other Hand, Produced a Marked Acceleration of Metabolism. (After Magnus-Levy, Ztschr. f. klin. Med.)

Obesity

Pathogenesis

Whenever the amount of energy derived from the food is greater than the amount of energy consumed by the body, a deposition of energy-containing material in the body takes place. The ability of the body to store proteins and carbohydrates is, however, limited, so that any considerable and long-continued excess of food leads to an accumulation of fat. Conversely, obesity is always due to the fact that the intake of energy in the food has exceeded the body expenditures.

It is common knowledge that excessive eating and lack of exercise tend to produce obesity. The change from an active muscular life to one of muscular inactivity, or the change from a plain fare to a rich and tempting diet, is a well-known cause of increase in weight. The reason for the increase under such conditions is obvious, for the changes described tend to cause a disproportion between the intake and the consumption of energy.

On the other hand, certain individuals grow fat despite the fact that they appear to eat moderately and appear to take an ordinary amount of exercise. The cause for the gain in such individuals requires further consideration.

Increased Caloric Intake.—In certain instances, such persons really eat more than would appear on superficial observation. The value of food as an energy-carrier depends not upon its bulk alone but upon its composition as well. When a gram of fat is burned in the body it yields approximately 9.3 calories, and when a gram of protein or starch is burned it yields approximately 4.1 calories, whereas cellulose and water furnish no available energy to the body. Foods containing much water or much cellulose, therefore, contain relatively little energy, whereas fats, oils, sugars, and starchy foods are heavy carriers of energy. The person who grows fat, despite the small bulk of food eaten, is often one who chooses the energy-containing foods out of a varied menu, and prefers sweets, pastries, bread and butter to salads, fruits and green vegetables. Despite the fact that he appears to eat moderately, he may yet be taking a rich diet when measured in calories.

Diminished Exercise.—The energy consumed in exercise may be also misjudged. The energy requirements of a man of moderate weight (70 kilos) are estimated by Magnus-Levy about as follows:

Basal metabolism	1,600	calories per day
At rest in room	2,200	" " "
Light work	2,600	" " "
Moderate work	3,100	" " "
Heavy work	3,500	" " "

It is certain, however, that the energy consumption cannot be measured by the amount of external work performed, for certain individuals, especially those trained, are able to accomplish a given task with a minimum number of movements. Furthermore, while the nervous, restless individual is constantly making useless movements and does not relax his muscular tension even on sitting down, the phlegmatic person may seize every opportunity to relax, to rest and to sleep. It is apparent, therefore, that in estimating the consumption of energy one must take into account the total number of movements and the muscular tension, and not rely solely upon the work accomplished.

Constitutional Obesity.—Yet even when the amount of food is estimated from its caloric content and this is compared with the total muscular activity, there may still be individuals who grow or remain unaccountably fat. Von Noorden, particularly, has cited cases of obesity, where, despite a considerable restriction in the total calories taken per day and despite the fact that the individual was taking a prescribed amount of exercise, no loss of weight occurred over a considerable period of observation. Such cases, though admittedly rare, have raised the question whether obesity may be due, in certain instances, *not to a fault in eating or in exercise, but to some more fundamental disturbance in metabolism,* which enables obese persons to get along and to accomplish tasks with a smaller expenditure of energy than is normal. In other words, may not obesity be due to an unusually low basal metabolism, to a relatively small expenditure of energy for a given amount of muscular exercise, or finally to an unusually low production of heat after the ingestion of a given amount of food?

Up to the present time no definite proof has been furnished that such a fundamental alteration in metabolism is an important cause of obesity. The increased production of heat normally observed after eating food is also present in obese persons, although it is said by some to be less in quantity. The amount of heat liberated by a given muscular exercise is difficult to standardize, but there appears to be no reason for assuming that work is accomplished more economically by fat than by lean individuals, except in the sense that the former tend to avoid unnecessary effort and movements. Indeed, on account of their heavier weight, it seems probable that fat persons expend more energy in executing a given movement than do those who are thinner.

Basal Metabolism in Obesity.—The basal metabolism of obese individuals has been determined repeatedly in order to see if this differed from the normal. We have already pointed out the difficulties encountered in making comparisons of the basal metabolisms of different normal individuals. These difficulties are further increased when one attempts to compare the obese with the normal, for the reason that the former has a large amount of inactive fat tissue in his body. If the metabolism

per unit of weight be used as a standard of comparison, the fat person has a low metabolism. If the metabolism be compared with the body height, the fat person has a basal metabolism which is, if anything, in excess of the normal. Finally, if the metabolism per unit of surface area be used as a basis of comparison, it is found that fat individuals have a normal or somewhat reduced basal metabolism as compared with the average normal. Probably even here, however, as Means has pointed out, the metabolism per unit of surface area may be strictly normal if the body surface be correctly estimated. In any case it is certain that the basal metabolism of obese individuals is little, if any, lower than the lowest normal limits. A low basal metabolism, therefore, can hardly be more than a contributing cause for an increase in body weight.

Obesity after Castration.—The fact that, in certain instances, animals as well as men gain weight after castration has led to a number of investigations as to the cause of this form of obesity. According to the observations of Loewy and Richter, the basal metabolism of the dog is lowered after castration. Others, however, have found that such a lowering is not constant, and that, furthermore, the tendency to obesity does not necessarily run parallel to the changes observed in the basal metabolism. Excision of the pituitary gland in young dogs tends to cause obesity, and Benedict and Homans have shown that it also causes a definite lowering of metabolism. On the other hand, Means found a rather high basal metabolism in a patient suffering from obesity of pituitary origin.

Obesity Not Due to Reduced Metabolism Alone.—It seems evident, therefore, that the laying on of fat cannot be definitely attributed to any constitutional reduction of metabolism thus far demonstrated in obese individuals. It should be remembered, however, that even a slight discrepancy between the intake and the consumption of energy, if continued over a long period of time, will eventually lead to a considerable deposit of fat in the body. Thus von Noorden has estimated that an intake of 200 calories daily, such as is contained in two glasses of milk, over and above what is just required to supply the needs of the body, would at the end of a year cause an increase of about 24 pounds in weight. With our present standards it would be quite impossible to recognize such a slight variation as pathological, for the variations among different normal individuals are greater than this.

Regulatory Effect of Appetite.—The view that obesity is due solely to some slight but long-continued deviation from the normal total metabolism, is, however, rendered improbable by the fact that far greater variations in total metabolism not infrequently result from a change in the amount of muscular exercise habitually taken without causing a progressive alteration in the body weight. If, for example, an individual who has been doing heavy work with an expenditure of 3,500 calories per

day changes to light work with an expenditure of 2,600 calories per day, his weight may increase for a time, but after a while it becomes stationary at the new level, evidently because a change in appetite has caused him to reduce the food intake, so that the latter just covers the reduced level of expenditures. The regulatory effect of appetite may also be noted by one who follows his weight from day to day. A series of unusually large meals often causes an increase of two or more pounds in weight. This gain may last for a few days but it gradually disappears owing to a lessened appetite. The regulatory effect of appetite is also evident when one attempts to increase the body weight by adding certain articles to the diet. If, for example, two glasses of milk with their 200 calories are taken each evening, these do not ordinarily cause a gain of twenty-four pounds at the end of the year. As the individual begins to gain in weight the appetite is lessened and less food is eaten at the regular meals.

Disturbed Sense Control of Food Intake.—It is probable, therefore, that one, and perhaps the most important, cause of obesity is a disturbance of the senses that control the intake of food, i. e., hunger, appetite and the sense of repletion. Owing to this disturbance, the food intake is not adjusted so that it just covers the requirements of the body. Instead of just meeting the body needs, the food is taken in excess of these needs and energy-containing material accumulates in the body. Since we have no definite knowledge as to the manner in which our sensations normally regulate the intake of food, it is difficult to discuss the pathological changes in these sensations that may lead to obesity. The fundamental control of food intake probably depends upon some chemical changes within the body. If this be so, it follows that this control might readily be disturbed both in metabolic diseases and in disease of the glands of internal secretion. The association of obesity with other metabolic disorders, such as gout and diabetes, and its association with disorders of the hypophysis and sex glands may be explained in this manner. From this standpoint, the lesser variations observed in the basal metabolism of different individuals under normal or pathological conditions lose much of their significance as an essential cause of obesity, for these lesser changes in the total metabolism may readily be covered by variations in the food intake. Only when the energy metabolism is markedly disturbed, as it is in certain cases of thyroid disease, does it play a preponderating rôle in modifying the body weight.

In practice it is well known that changes in weight can only be brought about by overcoming the natural instincts of the individual which guide his intake of food. To gain weight the intake must be "forced" with a high caloric diet. To lose weight the diet must be deficient in its total energy. A restriction or an addition of certain articles in the diet often causes no gain or loss, for the individual involuntarily modifies the amount of other foods taken.

Effect on Body Functions

Obesity affects the body in various ways. The thick layer of subcutaneous fat lessens the capacity for heat dissipation through radiation and conduction. So long as the fat person is inactive and the surrounding temperature is cool, the dissipation of heat through the skin does not differ materially from the normal. If, however, the heat that is produced within the body be increased by muscular exercise, and particularly if heat losses are made difficult by exposure to a warm and moist atmosphere, then differences from the normal heat elimination become apparent. Where the lean individual is still able to maintain his normal temperature mainly by an increased radiation and conduction, the fat person cannot lose sufficient heat from the body by these means alone. Consequently he perspires. This excessive sweating of fat individuals aids them in maintaining a normal body temperature under adverse circumstances. At the same time it indicates that the limits of their regulatory power against overheating are more restricted than the normal. When the conditions for heat dissipation are still more unfavorable, the fat person may show an abnormal rise of body temperature while the lean individual is still able to withstand the severe test. Obesity, therefore becomes a predisposing factor in heat stroke.

Restriction of Liquids.—Fat individuals usually drink considerable quantities of water. Possibly they feel an instinctive need of liquids, in order that unusual quantities of water should be available for the regulation of the body temperature by sweating. Restriction of liquids may cause an immediate and considerable loss of weight. This early loss, however, appears to be due to a drying out of the body and not to a combustion of fat. At present there is no positive evidence that drink restriction influences the metabolism of fat persons in any fundamental way. Its practical value in the treatment of obesity is still uncertain, but it would seem that any value that drink restriction may possibly possess is attributable not to a change in the fundamental metabolism, but to an effect upon the appetite or upon the capacity for muscular exercise. It should be remembered, however, that drink restriction lessens the amount of water that is available in the body for the purpose of temperature regulation and that, furthermore, a marked restriction in the intake of fluid may affect the functions of the kidney unfavorably. For these reasons rigid drink restriction requires caution.

Indisposition to Exercise.—Fat persons tend to restrict the amount of exercise taken. As we have seen, this lack of exercise is a factor in the pathogenesis of obesity. Obesity, however, also diminishes the inclination to exercise. As a person puts on weight he grows less restless and energetic, a fact that is utilized in the fattening treatment of nervous individuals. The disinclination to exercise is favored also by excessive

perspiration, and fat persons avoid exercise partly because the free perspiration is disagreeable. Since the fat person usually takes but little exercise, his voluntary muscles become small and weak. The heart is similarly affected. Its strength is diminished both by the lack of exercise and by fatty deposits in and about the myocardium. Thus the fat person eventually becomes incapacitated for violent exercise, partly because his voluntary muscles are untrained and his heart muscle weakened, and partly because he must move an unusually heavy body. The milder types of dyspnea that follow the exertions of fat persons are due to these causes. In other and more serious cases, however, there may be additional reasons for cardiac insufficiency, such as coronary sclerosis, chronic hypertension, or myocardial disease. The nutritional disturbances in obesity apparently predispose to changes in the structure and function of the blood vessels.

Starvation

Complete starvation is rarely seen. It may be due to an inability to obtain food as when an individual is lost in a barren region. It may result from voluntary fasting for religious, fanatical, therapeutical, or scientifical purposes, or in certain psychoses. Finally, complete starvation may be the result of disease, such as complete obstruction of the esophagus, constant vomiting, etc. The metabolic changes during complete starvation have been studied with great care by a number of scientific investigators. These studies are of considerable interest to clinicians, not only because complete starvation is occasionally encountered in the clinic, but because partial starvation is relatively frequent, and studies of complete inanition serve to throw light upon the more common condition of partial inanition.

Prolonged Fasts.—The effects of starvation are greatly influenced by the amount of water that is allowed. Without water, life is much shortened and the suffering from thirst is intense. On the other hand, if water be supplied to the body, complete starvation is not particularly distressing. Complete fasts of thirty and thirty-one days have been made under conditions which guaranteed the absolute character of the fast; and longer fasts of forty days or more have apparently been accomplished under less rigid control. Indeed, dogs have been deprived of all food for over one hundred days and yet have recovered from the prolonged starvation.

The most celebrated of the professional fasters was Succi. He subjected himself to ten or more separate periods of starvation, some of these being under strict scientific control. On one occasion he is said to have starved for 45 days, but in this case accurate control was absent. Probably the most careful study of a prolonged fast is that made by F. G. Benedict at the Nutrition Laboratory of the Carnegie Institution

in Boston. The following data are derived mainly from this (Fig. 63) and from a previous study of starvation by Benedict and Carpenter.

Reduced Rate of Total Metabolism.—The rate of total metabolism during fasting is reduced. This reduction is due in part to the languor associated with starvation, which causes the individual to restrict his exercise so that the heat derived from this source is diminished. In addition, there is a moderate reduction in the basal metabolism. Benedict found

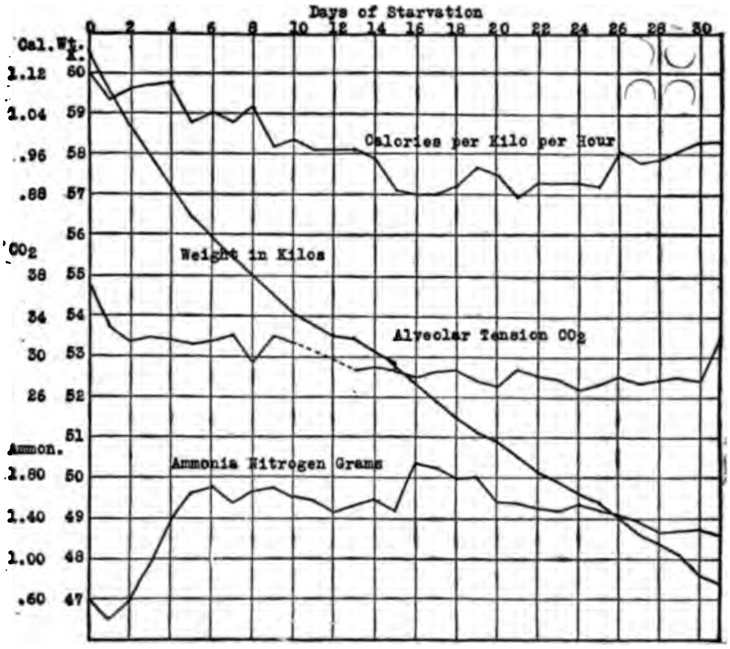


Fig. 63.—Effect of Complete Starvation upon the Body Weight, the Rate of Metabolism, the Tension of Carbon Dioxid in the Alveolar Air, and the Excretion of Ammonia in the Urine. Note that the Weight Falls Rapidly at First, that the Metabolism per Unit of Body Weight Falls to a Minimum about the Sixteenth Day, and that the Acidosis Is Shown Both by the Diminished Tension of Carbon Dioxid in the Alveolar Air and by the Increased Excretion of Ammonia in the Urine. (Redrawn and simplified from Benedict, Science.)

that the heat produced at night fell from about 26.9 per kilo per 24 hours to a minimum of about 21.1 calories, the latter being observed on the sixteenth day of the fast. Such a reduction does not approach that observed in hibernating animals where the metabolism may be reduced to one-fifth or even one-twentieth of the normal. In this latter condition, the extraordinary reduction is almost certainly due to the fall of body temperature and is due only in small part to the associated starvation. The moderate reduction of metabolism observed in starving men has, indeed, been attributed by some solely to the loss of weight and the diminution of body surface, but Benedict found that the fall is greater than could be accounted

for in this manner. Furthermore, after the seventeenth day of starving his subject showed a slight increase in the rate of metabolism per unit of body weight, and this continued for the remainder of the fast. This relative increase in metabolism during the later days of starvation, like the relative diminution during the earlier days, apparently depends upon some change in the internal metabolic stimuli, being similar, therefore, to the increased rate of metabolism observed after the taking of protein food.

Combustion of Body Constituents.—The rate at which the different constituents of the body are burned during complete starvation has been computed by various investigators. During the first day of starvation approximately 100 grams of glycogen are consumed, the amount depending upon the nutritive state of the individual when the fast began. The amount of glycogen burned falls rapidly during the early days of fasting, owing to the depletion of the glycogen reservoirs. In Benedict's subject, L., the glycogen consumption had reached a very low level on the fourth day, and after the thirteenth day no further glycogen consumption appeared to take place. The starving body is, therefore, soon thrown on a fat-protein metabolism. This is evident from the change in the respiratory quotient which falls from over 0.8 on a mixed diet to approximately 0.7, the respiratory quotient of fat combustion. The protein disintegration varies in different individuals and in the same individual at different periods of the fast. Between 40 and 75 grams of protein are consumed daily. As the glycogen reservoirs are depleted the consumption of protein increases, but in the later periods of starvation it falls again.

Loss of Body Weight.—Fasting produces a gradual and continuous loss of body weight. The loss at first is relatively rapid, being in the neighborhood of two pounds per day. The rate of loss soon lessens, however, and eventually less than one pound is lost daily. This loss of body weight depends not only upon a combustion of glycogen, fats and proteins, but also upon variations in the water content of the body. The muscles and parenchymatous organs contain 70 per cent or more of water and the adipose tissues from 15 to 30 per cent. As these tissues disintegrate it is to be expected that the water which they contain will be lost from the body. The rapid loss of weight at the onset of starvation is, however, so great that it cannot be due to a disintegration of tissues alone. Excess water to the amount of four pounds may be lost during the first five days of starvation. This rapid loss of excess water during the earlier days of complete inanition is associated with an equally striking loss of chlorids from the body. It is not improbable that the two go together; for, as we shall see (page 429), a restriction in the chlorid intake without any other change in the diet may in certain normal individuals cause reductions of weight from water losses. Later in the fast the

water losses, according to Benedict, fail to keep pace with the tissue disintegration, so that the proportionate amount of water in the body becomes increased. Analyses of the bodies of animals that have died of starvation also show a watery condition of the tissues.

Acidosis.—Finally, complete starvation is accompanied by a more or less marked acidosis, which develops as the glycogen reservoirs become exhausted and the body is thrown on a fat-protein metabolism. Acetone bodies appear in the urine and acetone is eliminated in the expired air. Other evidences of acidosis such as an increase of ammonia in the urine and a reduced tension of carbon dioxid in the pulmonary alveoli are present. A discussion of the general nature of acidosis and of the conditions which lead to the formation of acetone bodies must be deferred for later consideration (pages 248-291).

Partial Inanition

By partial inanition we mean that the amount of energy supplied is insufficient to meet the needs of the body. Disturbances of nutrition that depend upon a deficiency in specific food constituents will be discussed in later sections. Partial inanition may be due: (1) to an increased consumption of body material; (2) to a lessened supply of available food; or (3) to a combination of these conditions.

Lessened Supply of Food.—A lessened intake of food may result from poverty, poor appetite, or the fear of pain or other discomforts after meals. A lessened supply of food to the tissues may also be due to some gross fault in the digestive apparatus, as when there is an obstruction in the esophagus, pylorus or intestines, or when the intestinal absorption is seriously impaired owing to advanced intestinal or pancreatic disease. In the severer forms of diabetes mellitus the starches, though digested and absorbed, cannot be utilized. Even when the patient eats and absorbs unusual quantities of food, the tissues may yet be starving.

Increased Metabolism; Disturbances of Appetite.—An excessive metabolism may result from violent muscular exercise. In normal individuals this is usually accompanied by an increased appetite, so that no serious loss of weight follows. If, however, as in delirium tremens, the appetite is also disturbed, then the excessive muscular activity causes a very rapid loss of weight. In exophthalmic goiter the metabolism is also increased, not only because of the high basal metabolism, but because the restless activities of the patient heighten the metabolism by muscular movements. Fevers increase the basal metabolism. The total energy consumption during fever, however, is usually no greater than in a normal individual who is doing light work or moderate work. If we assume, for example, that the resting metabolism for a given individual is 2,200 calories per day and that this is increased forty per cent owing to an infectious fever, then his metab-

olism would become about 3,000 calories daily. This is not greater than the metabolism of the same individual during moderate work. The partial starvation and the resulting loss of weight that so often accompany febrile infections cannot, therefore, be attributed to any remarkable increase in the rate of metabolism, but are due in the main to the fact that such patients do not cover their energy requirements by a sufficient intake of food. The absence of appetite plays an important part in causing the loss of weight during infections.

It is evident, therefore, that in the pathogenesis of partial inanition as in the pathogenesis of obesity, disturbances of appetite must always be given consideration. Particularly is this true of those thin, weak and often nervous individuals who resist all attempts at fattening. Just as the appetite in obese persons tends to regulate the body weight at a high level, so in these individuals the appetite tends to regulate the body weight at a low level. The addition of a few fattening articles to the diet is often followed by a loss of appetite for and a lessened intake of other foods, so that the body weight remains almost stationary. Only by a well-planned diet of high total energy and by an energetic forcing of the appetite can any considerable gain in weight be accomplished.

Secondary Effects of Chronic Malnutrition.—Chronic malnutrition, from whatever cause, exerts a number of secondary effects upon the individual. He often feels weak and he fatigues easily after any unusual effort. Increased nervousness is not only a cause of chronic inanition, but it is also one of its effects. The fattening treatment for nervousness is based on this fact.

It should be pointed out, however, that moderate degrees of thinness like moderate degrees of obesity are often compatible with perfect health. Only when emaciation becomes excessive is it in itself an indication for therapeutical interference. On the other hand, when thinness is accompanied by other functional disturbances, such as weakness and nervousness, attempts should be made to relieve these symptoms by causing a gain in weight.

The Protein Metabolism

The proteins taken in the food are broken down in the gastro-intestinal tract by a series of cleavages into simpler nitrogenous bodies. In the stomach peptones and proteoses are formed, and in the intestines these are further decomposed by the pancreatic trypsin and the intestinal erypsin into the amino acid building stones of which proteins are composed. The amino acids are absorbed by the intestinal mucosa and after absorption they are carried in the blood to various tissues (Folin), where they may either be still further disintegrated or may be utilized as building stones from which the characteristic body proteins are built up.

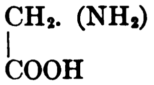
The Protein Building Stones

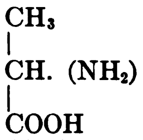
When proteins are completely hydrolyzed, whether by acids, by alkalis, by ferments or by steam, a series of compounds known as amino acids are obtained. These are the building stones of the protein molecules. Amino acids are characterized by possessing the acid radical —COOH and the amino radical —NH_2. In the amino acids obtained from proteins the amino group is attached to the carbon atom contiguous to the acid radical. It occupies the so-called *alpha* position in the carbon chain. The characteristic group in these amino acids is, therefore, as follows:

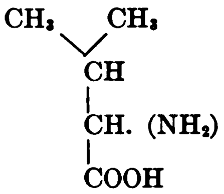
$$\begin{array}{l} CH.NH_2 \\ | \\ COOH \end{array}$$

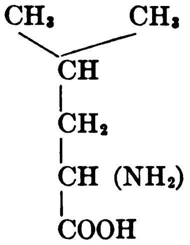
By virtue of its —COOH radical the amino acids may combine with bases, thus acting as an acid. By virtue of its —NH_2 group it may combine with acids, thus acting as a base.

Important Amino Acids.—Of the eighteen or more amino acids that have been isolated from proteins the more important will now be enumerated. The simplest of these are those in which the amino radical has been added to fatty acids.

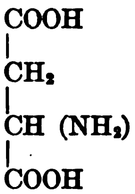

Glycocoll

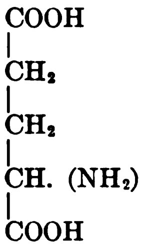

Alanin


Valin

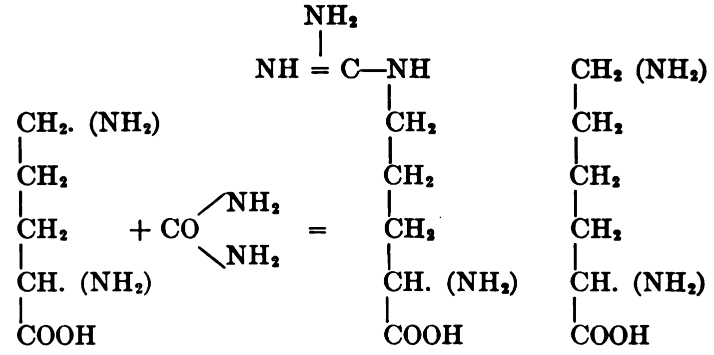

Leucin

As examples of dicarboxylic amino acids with pronounced acid qualities we have:


Aspartic acid

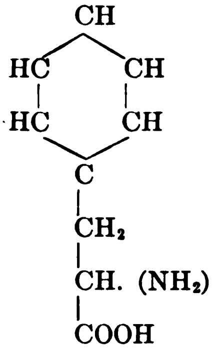

Glutamic acid

As examples of diamino acids we have ornithin and lysin, the former of which combines with urea to form arginin:

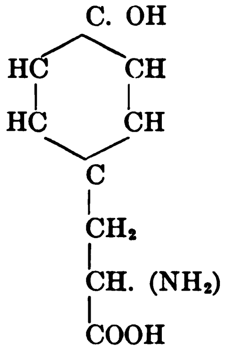


Ornithin Urea Arginin Lysin

Combinations with the benzene ring are represented in phenylalanin and tyrosin:

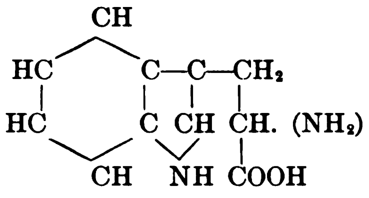


Phenylalanin

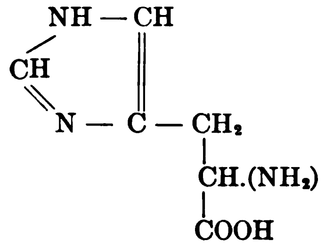


Tyrosin

Combinations with other complex rings are represented in tryptophan and histidin, the former of which is an indol derivative:



Tryptophan



Histidin

Finally sulphur is contained in proteins in the form of cystin, which is related to the amino acid serin:

$$
\begin{array}{llll}
CH_2OH. & CH_2SH & CH_2 - S - S - CH_2 & \\
| & | & | \qquad\qquad\quad | & \\
CH.(NH_2) & CH.(NH_2) & CH.(NH_2) \quad CH.(NH_2) & \\
| & | & | \qquad\qquad\quad | & \\
COOH & COOH & COOH \qquad\quad COOH & \\
\text{Serin} & \text{Cystein} & \qquad \text{Cystin} &
\end{array}
$$

Methods of Combination.—The manner in which these building stones are linked together to form the highly complex protein molecules is in part understood. Two types of combination have just been noted: (1) the formation of arginin by the union of urea and ornithin; and (2) the linking of two cystein molecules to form cystin. More important and of more general application are the complexes formed by the union of the alkaline amino group of one acid with the acid group of another. For example, two molecules of glycocoll may unite in this manner to form glycylglycin:

$$
\begin{array}{ccccccc}
 & & & & & CH_2.NH_2 & \\
 & & & & & | & \\
CH_2.NH_2 & & CH_2.NH_2 & & CH_2.NH. & CO & \\
| & + & | & = & | & & + H_2O \\
COOH & & COOH & & COOH & & \\
\text{Glycocoll} & & \text{Glycocoll} & & \text{Glycylglycin} & & \text{Water}
\end{array}
$$

By this type of reaction any two amino acids may unite, thus forming a dipeptid. Since the latter contains a COOH group at one extremity and an NH_2 group at the other, it may unite with further amino acids to form tripeptids, tetrapeptids, etc. A large number of polypeptids have been formed synthetically by this manner of linking. When the amino acid contains two NH_2 groups (lysin) it may combine with the COOH groups of two other amino acids. When it contains two COOH groups (glutamic acid) it may combine with the NH_2 groups of two other amino acids. In this way branched chains may be formed. Various other types of combination are theoretically possible.

Great Variety of Combinations.—Chemical analyses have shown that the different proteins contain different amounts of the various amino acids, and that certain proteins may even lack certain of the building stones that are ordinarily present in the proteins of the animal body. Even where no difference in the kind and amount of amino acids can be determined by analysis, proteins may still differ from one another by reason of the fact that the amino acids are arranged in different manners within the complex protein molecule. Indeed, an almost limitless number of such arrangements are theoretically possible. Proof of the existence of countless numbers of different proteins has been furnished in recent years by biological methods of study. These have shown not only that the proteins of an animal differ from the proteins taken in its

food, but that each species of animals has its own characteristic proteins which may be differentiated from those of every other animal species.

Amino Acid Requirements of the Body

The importance of the constituent building stones of the protein molecules, rather than of proteins as such, for the maintenance and growth of the body has been demonstrated by two types of experiment. In the first place, the nitrogenous requirements of the body may be satisfied by feeding mixtures composed of amino acids and simple combinations of the same that have been prepared outside of the body by a prolonged digestion of proteins. Such mixtures may be so far digested that they no longer give the biuret test for peptones. It is evident from these experiments that the body can synthesize its proteins from mixtures containing the constituent building stones or very simple combinations of the same.

Certain Amino Acids Necessary.—In the second type of experiment, it has been demonstrated that a protein which is deficient in certain of the usual building stones may fail to cover the bodily requirements.

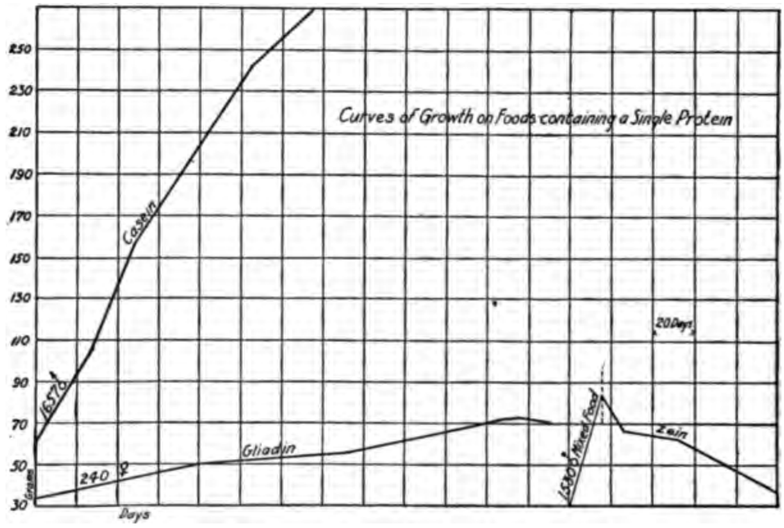


Fig. 64.—Typical Curves of Growth of Rats Maintained on Diets Containing a Single Protein. On the Casein (Devoid of Glycocoll) Satisfactory Growth Is Obtained; on the Gliadin (Devoid of Lysin) the Body Weight Increases But Little; on Zein (Devoid of Glycocoll, Lysin and Tryptophan) Weight Is Lost. (From Mendel, Jour. Am. Med. Assn.)

Osborne and Mendel have shown that it is possible to maintain rats in perfect health over long periods of time by feeding them certain isolated proteins in addition to the fats, carbohydrates and inorganic salts as they are present in the protein free fractions of milk. The casein of milk, the edestin of hemp seed, or the albumen or white of egg, are each able

to furnish all that is necessary to the body in the way of nitrogenous material. If, however, the protein gliadin that has been prepared from wheat is the sole protein used, adult animals may be maintained but young animals cease to gain in weight (Fig. 64). Gliadin is deficient in the amino acid lysin. When this is added to the above diet the growth of the young animals is promptly resumed. Similarly, if zein, the chief protein of corn, be the sole protein in an otherwise normal diet, young rats lose weight and adults fail in health. Zein is deficient in a number of amino acids and particularly in lysin, tryptophan, and glycocoll. If tryptophan be added to the zein diet, the body weight of adults is maintained but young animals still cease to grow. If tryptophan and lysin are both added, growth and maintenance become normal (Fig. 65). Finally, casein is deficient in glycocoll, yet the body require-

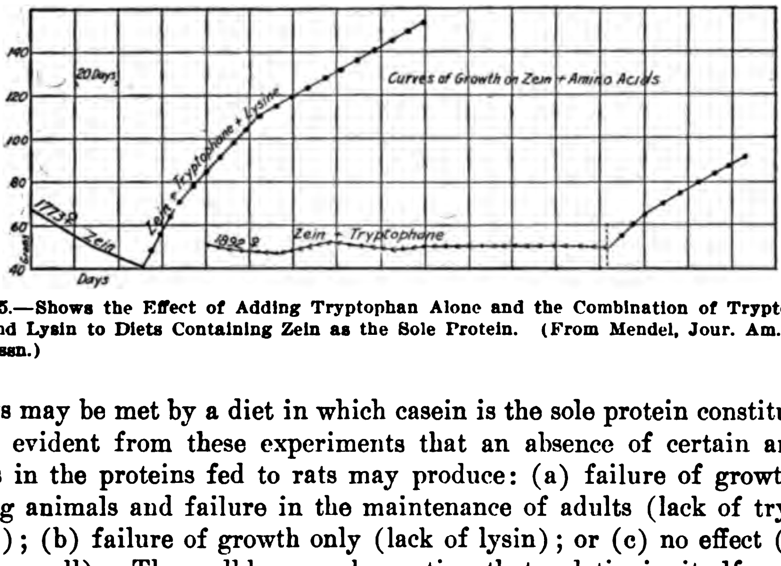


Fig. 65.—Shows the Effect of Adding Tryptophan Alone and the Combination of Tryptophan and Lysin to Diets Containing Zein as the Sole Protein. (From Mendel, Jour. Am. Med. Assn.)

ments may be met by a diet in which casein is the sole protein constituent. It is evident from these experiments that an absence of certain amino acids in the proteins fed to rats may produce: (a) failure of growth in young animals and failure in the maintenance of adults (lack of tryptophan); (b) failure of growth only (lack of lysin); or (c) no effect (lack of glycocoll). The well-known observation that gelatin in itself cannot supply the protein needs of the body is due to the fact that this substance is deficient in tyrosin, tryptophan and cystin.

Body Cannot Synthesize Most Amino Acids.—Since normal growth is impossible when certain of the amino acids are absent from the diet it is evident that the body is unable to supply this deficiency by constructing these protein building stones. In the case of lysin, tryptophan and cystin, this inability has been proven and the same is probably true of many others. Taylor states that we may, for the present, assume that, except glycocoll, all the amino acids must exist preformed in the proteins of the diet in amounts sufficient to offer the units needed for tissue building and repair.

Fortunately, the majority of proteins in common use, and particularly

those of animal origin, contain all of the requisite building stones; and when an individual is on an abundant diet of mixed proteins he is amply protected against any deficit in amino acids. If, however, the diet is very one-sided and if, in addition, the protein intake be not very abundant, a deficit of amino acids may lead to nutritive disturbances.

Nitrogenous Equilibrium

We have seen that the total energy metabolism is governed in large part by factors that are independent of the food intake. Any excess of food above the immediate requirements of the body leads to an accumulation of energy-containing material in the tissues, and, conversely, any deficit in the total food is made good by a consumption of material from these accumulations. The rate of nitrogenous metabolism, on the other hand, is governed primarily by the amount of protein in the food. When this is increased the excretion of nitrogenous waste becomes greater, and when it is diminished the excretion of nitrogenous waste lessens. Thus an equilibrium tends to become established between the intake and the output of nitrogenous substances, and the body maintains its content of nitrogen-containing material at a fairly constant level.

Retention of Nitrogen.—Nevertheless, some change in the amount of nitrogen in the body may be induced by changes in the diet. An abrupt change in the nitrogenous intake is followed by a less abrupt change in the output and some retention of nitrogen always accompanies the change from a poor to a rich protein diet, and, conversely, some loss occurs when the change is in the opposite direction. Indeed, some investigators (Lüthje) have induced a considerable increase of nitrogenous material in the body by giving large amounts of proteins and by protecting the proteins by large quantities of other foods, especially carbohydrates. The form in which this excess of nitrogen is retained in the body is not known, and it is not certain that the amount of living protoplasm can be increased by this method.

Nitrogenous retention also occurs, when, for any reason, there is an inherent need on the part of the body tissues and cells for proteins. In the growing child, during the muscular hypertrophy that accompanies training, and during convalescence from infectious and other wasting diseases, a retention of nitrogenous materials in the body usually occurs. This arises from an obvious need on the part of the tissues and in these cases the retained nitrogen is doubtlessly utilized in the construction of additional living protoplasm.

Protein Requirements of the Body

We have just seen that nitrogenous equilibrium may be established at different levels. The upper limit at which it may be established is

apparently governed solely by the ability of an individual to eat large quantities of protein food. On the other hand, if the protein in the diet be reduced below a certain point, the excretion of nitrogenous waste will exceed the intake, and there will result a negative balance and a continuous loss of proteins from the body.

Minimum Protein Metabolism.—During complete starvation from forty to seventy grams of protein are consumed by the body each day. This does not, however, represent the minimum protein metabolism; for if an individual eat abundantly of carbohydrates or of carbohydrates and fats, and at the same time abstain from all nitrogenous food, the nitrogen losses are much less than those which occur during complete starvation. Under these conditions of a "specific protein starvation," Landergren found that the nitrogen in the urine fell to about four grams per day, an amount which corresponds to a consumption of approximately 25 grams of protein daily. The ingestion of fat alone does not reduce the nitrogen losses to as low a level as does the ingestion of carbohydrates. In other words, fats do not "spare" proteins to the same degree as do carbohydrates.

Low Protein Intake and Nitrogenous Equilibrium.—A reduction of protein food has frequently been recommended as a general hygienic measure, and it is often used in the treatment of renal disease, diabetes mellitus, etc. Of immediate interest to clinicians, therefore, is the question as to what constitutes the minimum amount of protein that will suffice to maintain nitrogenous equilibrium and will prevent a loss of proteins from the body. Sivén succeeded in maintaining nitrogenous equilibrium on a diet that contained approximately 37 grams of protein daily, of which about 28 grams were apparently absorbed. This appears to be an unusually low level, and it is doubtful if all persons can be maintained in nitrogenous equilibrium on such a ration. In Chittenden's extensive experiments, nitrogenous equilibrium was maintained on diets which contained approximately 50 grams of protein daily. This is less than one-half of the 118 grams of protein which are contained in Voit's standard diet and it is about one-third that eaten by the majority of well-to-do individuals.

Whether such a reduced protein intake, even with the maintenance of nitrogen equilibrium, is advantageous as a general hygienic measure has been much discussed and is still unsettled. Many persons may certainly remain strong and in good health on such a diet and some believe that their efficiency is increased. On the other hand, any close approach to a physiological limit carries with it a certain amount of danger, for unusual conditions may at any time arise, in which it would be advantageous for the body to have at its disposal a larger quantity of protein. The intake of a quantity of protein that exceeds the minimum limit provides a factor of safety for such emergencies, and it may possibly be advantageous in other ways.

Protein Starvation

Protein starvation may result from a voluntary or involuntary restriction of the intake of protein food. Occasionally, one sees individuals who have been recommended to restrict their protein intake and have done so with such enthusiasm that they are evidently near or below the level at which a nitrogenous equilibrium can be maintained. Such patients complain of lassitude, weakness and early fatigue during work, and these symptoms rapidly disappear if the protein intake be increased. A restriction of the protein intake may also accompany general inanition. In such patients, however, the symptoms of the protein starvation are disguised by those of partial starvation.

We have already pointed out that the body is unable to synthesize most of the amino acids that make up the protein molecule. If certain of these be entirely absent from the diet the animal does not thrive. It is evident also that in conditions of low protein intake the effect will depend not alone upon the total quantity of protein consumed, but also upon its richness in each of the necessary amino acids. When the protein intake is low and when it does not contain a proper balance of the necessary amino acids, nitrogenous equilibrium can only be maintained when sufficient quantities of proteins are taken to cover the need of the body for each of these necessary building stones. Thus Thomas showed that when starch and sugar were taken in abundance, the following amounts of various protein mixtures in the natural foods were required to protect the body from protein losses:

Meat protein	30	grams	per	day
Milk protein	31	"	"	"
Rice protein	34	"	"	"
Potato protein	34	"	"	"
Bean protein	38	"	"	"
Bread protein	76	"	"	"
Indian corn protein	102	"	"	"

It is evident that the proteins of animal origin as well as those contained in rice and potatoes suffice to maintain the individual when taken in small quantities, whereas the proteins of bread and of Indian corn can supply the body needs only when they are taken in relatively large quantities. These differences are presumably due to the differences in composition of the proteins that occur in these natural foodstuffs.

Excessive Protein Destruction

It is obvious that when there is a gross disintegration of cells in the body the proteins in these cells will be broken down, and the protein

metabolism of the body will be increased by this added fraction. In the resolution of a pneumonic exudate, in the liquefaction of a purulent collection, in the disintegration of malignant tumors and in the serious damage of organs by disease (phosphorus poisoning, acute yellow atrophy of the liver), the total protein metabolism of the body will be increased by this excessive protein destruction.

Loss of Nitrogen in Fever, Etc.—In addition, it has frequently been noted that in fever, in some patients with exophthalmic goiter, and in certain cases of malignant disease, the excretion of nitrogen in the urine tends to exceed the intake of nitrogenous substances in the food. When efforts are made to maintain an equilibrium by feeding increased amounts of protein, the excretion of waste products also increases, and to such an extent that nitrogenous losses continue even when the intake of proteins is high. The doctrine that in such patients there is a pathological destruction of the body proteins will be considered more fully in the chapter on fever. It may be pointed out in this place, however, that the difficulty in maintaining nitrogenous equilibrium is due in part to an insufficient general nourishment of such patients. The increased total metabolism in fever and in exophthalmic goiter, combined as it often is with a poor appetite, leads to a chronic inanition, and when the body must subsist in part upon its own tissues, it is always more difficult to maintain nitrogenous equilibrium. An abundant diet, containing large quantities of carbohydrates, may cause nitrogenous equilibrium, or even nitrogenous retention, in patients who would otherwise suffer from nitrogen losses.

Nevertheless, it seems probable that, in fever at least, an abnormal disintegration of proteins may take place in the body. The anatomical degenerations of the cells, observed in fever, support this view. Furthermore, R. A. Kocher has shown that when a febrile patient is given sufficient nourishment to cover his caloric needs, and at the same time is very much restricted in his nitrogenous intake, his nitrogenous metabolism is not reduced to the same low level as is that of a normal individual. In the latter, such a specific protein starvation may reduce the excretion of nitrogen in the urine to 4.0 or even to 2.5 grams per day; whereas, under similar conditions, the excretion of nitrogen in the urine of febrile patients may be as much as 15 to 25 grams daily. It is evident, therefore, that an abnormal destruction of body proteins may take place without a gross death of the cells. That the protein losses may be overcome more or less completely by a suitable diet is a triumph of the therapeutical art. It does not alter the fact, however, that in certain patients with fever there is an abnormal disintegration of the body proteins.

Autolysis

If an organ removed from the body is kept at a temperature of 37° C. under conditions which preclude bacterial growth, a self-digestion of its

tissues takes place, owing to the action of the intracellular ferments which it contains. Glycogen is converted into sugar and the latter may undergo further changes. Fats and lecithin may also be decomposed. Of particular interest, in the present discussion, is the fact that the proteins are broken down into simpler nitrogenous compounds. The quantity of coagulable protein diminishes while the products of proteolysis, peptone, proteoses and amino acids appear in increased amounts. The sum of these processes whereby the organ digests itself is spoken of as autolysis.

When masses of cells die within the living body, their disintegration and removal are accomplished in part by the action of leukocytes and other wandering cells, and in part by an autodigestion similar to that which takes place when an organ removed from the body autolyses. The disappearance of a pneumonic exudate during resolution, the liquefaction of a purulent collection, the absorption of hemorrhages and the involution of the uterus after pregnancy are all due in large part to autolysis. Very severe hepatic degenerations, such as occur in acute yellow atrophy, phosphorus poisoning and related conditions, are associated with a marked self-digestion of the liver. It seems probable that serious damage to the hepatic cells has opened the way for self-digestion and that the latter may serve the useful purpose of removing dead material.

Autolytic Ferments in Living Tissues.—The intracellular ferments that are active in autolysis are probably also active, though to a lesser extent, in the living tissues, and they probably play an important rôle in the normal life processes of the cells. Their increased activity in dead or badly damaged tissues has been variously attributed to a change from the normal alkaline to a somewhat more acid reaction, to an absence of protective antiferments, to nutritional disturbances in the cells, etc. Autolysis may be accelerated in vitro by a variety of conditions. It is favored by a slightly acid reaction, and by the addition of earthy metals, manganous chlorid, colloidal metals, and other substances. Whether living and normal tissues may be subjected to excessive autolysis in the body is still uncertain; but such a primary increase in autolysis may possibly play an important rôle in certain pathological conditions. The severe hepatic degenerations have indeed been attributed to such a primary increase in the autolytic process, but it is equally probable that they are due to a primary damage to the cells with secondary digestion. According to Bronfenbrenner and to Jobling, however, the phenomena of acute anaphylaxis depend upon a rapid autolysis of the proteins normally present in the serum, owing to a removal of inhibitory substances.

When autolysis is rapid the blood and urine often contain the products of protein disintegration in increased amounts. In acute yellow atrophy of the liver, for example, peptones, proteoses, and various amino acids have been found in the urine, while leucin, tyrosin and lysin have been detected in the blood. In some cases, indeed, the quantitives of these substances

found during life and at autopsy have been so great that they must have been derived in part from other tissues than the liver. Similarly in phosphorus poisoning, leucin, tyrosin, phenylalanin, alanin and arginin have been detected in the urine, and often in considerable quantity. Probably, as we shall see, the remarkable amounts of amino acids which appear in these conditions are due not to the pathological autolysis alone, but to a simultaneous disturbance in the normal conversion of amino acids into urea.

Imperfect Decomposition of Amino Acids

Hepatic Disease, Etc.

Under normal conditions the formation of urea from the amino acids probably takes place in two stages. In the *first stage,* there is a deaminization of the acid with a liberation of ammonia.

$$\begin{array}{llcll} CH_3 & & & CH_3 & \\ | & & & | & \\ CH.NH_2 & + H_2O & = & CHOH & + NH_3 \\ | & & & | & \\ COOH & & & COOH & \\ \text{Alanin} & \text{Water} & & \text{Lactic Acid} & \text{Ammonia} \end{array}$$

The ammonia immediately combines with the carbonic acid always present in the body fluids. In the *second stage,* the ammonium carbonate thus formed is converted into urea, ammonium carbamate being an intermediary product:

$$\begin{array}{lllclcl} & & O.NH_4 & & O.NH_4 & & NH_2 \\ & & | & & | & & | \\ 2\,NH_3 + & H_2CO_3 = & CO & \longrightarrow & CO & \longrightarrow & CO \\ & & | & & | & & | \\ & & O.NH_4 & & NH_2 & & NH_2 \\ \text{Ammonia} & \text{Carbonic} & \text{Ammonium} & & \text{Ammonium} & & \text{Urea} \\ & \text{Acid} & \text{Carbonate} & & \text{Carbamate} & & \end{array}$$

This conversion of the amino groups of the amino acids into urea may certainly take place in the liver. To what extent other tissues of the body perform a similar function is not known, but it seems probable that the liver is not the only organ in the body in which such changes may occur.

Excess of Amino Acids in Urine.—We have just seen that in the severe hepatic degenerations, of which acute yellow atrophy may be taken as a type, the urine contains large quantities of amino acids and particularly of leucin, tyrosin, etc. These substances are formed from the increased autolysis of the liver and probably from other organs of the body. The total nitrogenous metabolism in these diseases is usually increased over that of a normal individual taking the same food. On the other hand, when large quantities of proteins are eaten by a normal individual, his nitrogenous metabolism certainly exceeds that ordinarily present in these diseases, and yet no excessive amounts of amino acids appear in his urine. It is

obvious, therefore, that in severe liver degenerations there is a qualitative as well as a quantitative deviation from the normal protein metabolism. The deamination of the amino acids is disturbed.

Amino acids also appear in the urine in somewhat increased quantities in certain fevers, and particularly in typhoid, scarlet fever, pneumonia and variola. They also appear in hepatic cirrhosis. In these conditions also there appears to be some failure on the part of the body to deaminize the amino acids derived from protein hydrolysis. Whether this is due solely to hepatic changes or whether it represents a general disturbance in the tissue functions throughout the body is still uncertain.

Cystinuria

The inability to decompose amino acids may be restricted to certain of these acids only. The appearance of considerable cystin in the urine, for example, is due to a specific failure to decompose this product of protein disintegration. In the normal individual cystin is converted: (1) into the taurin of the bile; (2) into sulphates which are eliminated by the kidneys; and (3) into the neutral sulphur of the urine, a trace of which may be in the form of cystin or cystein. In patients with cystinuria, however, a considerable proportion of the cystin derived from the cleavage of proteins is excreted as such. This may produce no symptoms, or again it may give rise to a urinary sediment and to urinary stones composed of cystin. If the urine be kept alkaline, the cystin is no longer precipitated, and in this manner the patient may be relieved of his symptoms.

The amount of cystin excreted by such patients can be reduced by restricting the intake of protein food, but even during protein starvation the urinary excretion of cystin usually continues. In this case it is derived from the disintegration of the body proteins.

Diaminuria

In some, but not in all, patients with cystinuria there is an associated defect in the metabolism of other amino acids. Lysin is eliminated as the diamin, cadaverin, and ornithin derived from arginin is eliminated as the diamin, putrescin:

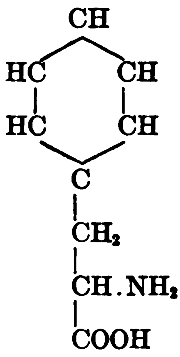
$CH_2.NH_2$	$CH_2.NH_2$
|	|
CH_2	CH_2
|	|
CH_2	CH_2
|	|
CH_2	CH_2
|	|
$CH.NH_2$	$CH_2.NH_2$
|	
$COOH$	
Lysin	Cadaverin

Ornithin	Putrescin
$CH_2.NH_2$	$CH_2.NH_2$
$\vert$	$\vert$
CH_2	CH_2
$\vert$	$\vert$
CH_2	CH_2
$\vert$	$\vert$
$CH.NH_2$	$CH_2.NH_2$
$\vert$	
$COOH$	

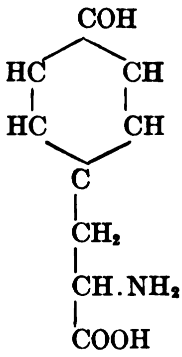
In addition to their occurrence in the urine as a result of metabolic disorders these diamins may also occur as a result of bacterial activity in the intestines, and they have been found in dysentery, cholera and other severe forms of enteritis. Although these particular amins are practically innocuous, it should be recalled that other amins, which may possibly be formed by analogous reactions in the intestines as a result of bacterial activity, are highly poisonous. These latter have been discussed more fully in the paragraphs on intestinal auto-intoxication.

Alcaptonuria

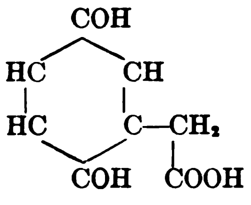
Alcaptonuria has long been recognized as a relatively rare and harmless metabolic disturbance which is characterized by a urine that darkens under the combined influence of alkalis and oxygen and that reduces copper solutions in the same manner as glucose-containing urine. The substance which gives to the urine these properties is called alcapton or homogentesic acid. It is derived from the protein-building stones, tyrosin and phenylalanin, and it is related to hydroquinon and pyrocatechin, which substances are responsible for the darkening that occurs when the urine of patients poisoned with carbolic acid is exposed to the air. The relation between these substances is shown in the following chemical formulae:



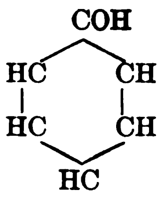
Phenylalanin



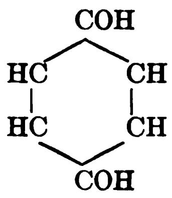
Tyrosin



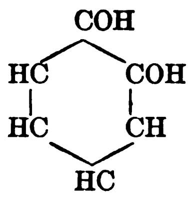
Alcapton



Carbolic Acid



Hydroquinon



Pyrocatechin

The amount of homogentesic acid excreted by patients with alcaptonuria is increased by a diet rich in proteins, is diminished by a protein-poor diet, but continues even during starvation. Under the last circumstances it is derived from the metabolism of the body proteins. The amount of alcapton in the urine can also be increased by feeding phenylalanin or tyrosin. Possibly, it is formed normally in the body as an intermediary product of the catabolism of these substances. If this be so, the cause of alcaptonuria would appear to be the lack of that ferment which normally decomposes the benzene ring present in homogentesic acid. In consequence the latter is eliminated in the urine.

Ochronosis

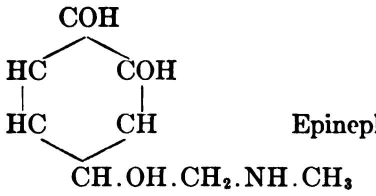
The property possessed by alcapton and by related substances of changing readily into a dark pigment is of considerable interest in connection with the production of certain pathological pigmentations in the body. In the rare condition known as ochronosis, the cartilages of the body become dark owing to the formation of a dark pigment. In certain cases, not only the cartilages, but also the fibrous and bony tissues, the blood vessels, the skin, the sclera and the nails become darker and melanotic pigment is excreted in the urine. Beddard and Plumtre have recently (1912) collected thirty cases of ochronosis from the literature. In fourteen of these the condition was associated with alcaptonuria, while in nine others it was associated with a long-continued absorption of carbolic acid, as, for example, when dressings containing this antiseptic had been used on open ulcers for a long time.

Melanin

The relation of black pigment formation to aromatic and other derivatives of protein catabolism is, however, of far more general application than in the pigmentations of ochronosis. The French chemist, Bertrand, showed that the reddening and subsequent blackening of certain mushrooms are due to an oxidizing ferment which acts particularly on tyrosin, and to which the name of tyrosinase has been given. A similar reaction is responsible for the blackening of various fungi and plants, for pigment deposits in certain of the lower animals and for the formation of the inky

fluid that is thrown out by cuttlefish. Gessard found that the melanotic tumors of the horse contained a tyrosinase which acted upon a chromogen of this type. Alsberg obtained an oxidizing ferment from a melanotic sarcoma of man which darkened solutions of pyrocatechin. Indeed, it seems not improbable that various black pigments normally present in the body, such as those in the skin of the negro, the choroid, etc., are due to the local action of a ferment of this type upon tyrosin or other protein-building stones (tryptophan), that either arise in, or are carried to the pigment cells.

Epinephrin.—Of particular interest is the fact that epinephrin, an active principle derived from the adrenal gland, is chemicaly related to tyrosin, and that it may yield dark pigments when acted upon by ferments of this class:



Epinephrin

Addison's Disease.—The pigmentation of the skin and other tissues which occurs in Addison's disease is doubtlessly due to a reaction similar to that described above. Whether this abnormal formation depends upon an excess of tyrosinlike substances in the body fluids or whether, as Bittorf believes, it is due to a local increase of the specific ferment in certain cells of the body, requires further study.

Diseases Due to Deficient Diets

We have seen that the total energy taken in the food is so guided by the appetite and related sensations that it approximately covers the body needs; whereas the intake of protein is usually in excess of these needs, the excess of nitrogenous material being for the most part decomposed and eliminated. This excess provides an element of safety in the diet. If the amount or character of the protein intake be insufficient, disturbances of growth and maintenance result. Not only proteins but a variety of other substances are habitually taken in the food in excess of the minimum body requirements. These excesses may cause a limited storage in the body, but beyond this limited storage the excess is excreted either unchanged or after having furnished energy to the body. If, for any reason, the intake of these substances falls below a certain minimum, nutritive disturbances may result.

Such nutritive disturbances do not appear immediately, for a certain amount of the substance that is cut out from the diet is usually already

present in the tissues, and the body clings tenaciously to such stores when the further supply is limited. Nutritive disturbances due to such specific deficiencies in the food are most apt to occur, when, as among the poorer classes, in institutions, and on expeditions, the diet is restricted and one-sided. Since the growing organism utilizes various substances for the construction of new tissues, it is more sensitive to deficiencies in the diet than is the adult. To the farmer and stockraiser the problem of dietetic deficiencies assumes considerable practical importance, for a maximum growth of animals cannot be obtained if the food is deficient in certain of its constituents.

Inorganic Salts

The tissues and body fluids contain a mixture of mineral substances. Although these furnish no energy to the body, they are essential for the performance of the normal body functions. McCollum and Davis found that growing rats were exceedingly sensitive to alterations in the composition of the salt mixtures taken in the food. Properly balanced mixtures containing sodium, potassium, calcium, magnesium, iron, chlorids, and phosphates were found to supply the salt requirements.

Sodium Chlorid.—Sodium chlorid is usually taken by man in considerable quantities, 10 grams or more being the ordinary daily portion. It is certain, however, that this amount is far greater than what is absolutely required, for during starvation the daily salt output sinks below 0.5 gram, and patients have been maintained for long periods of time on 2 to 4 grams daily with no apparent deleterious effect. For limited periods the amount taken may be reduced below this, but the exact minimum requirements for indefinite periods are not known.

Calcium and Phosphorus Compounds.—The mineral substances present in bones consist of fifty per cent or more of calcium phosphate with lesser amounts of calcium carbonate and magnesium phosphate. Growing as well as adult animals require these salts in the food, the P_2O_5 requirements for adult men being in the neighborhood of 3.4 grams daily. If the diet does not furnish a sufficient amount of calcium or of phosphorus compounds, nutritive disturbances in the bones appear. The disturbances in bony metabolism that are found in rachitis and in osteomalacia are not due to a lack of calcium and phosphorus compounds in the diet. Possibly, as some have maintained, an insufficient absorption of mineral substances may play a part in the pathogenesis of these diseases, but it seems more likely that the essential disturbance lies within the body, and that the bones are unable to utilize the salts that have been absorbed.

Iron Requirements of the Body.—Iron forms an essential constituent of hemoglobin. The normal body husbands its supply of iron with considerable care. Large amounts of hemoglobin, containing 100 to 200 mg. of iron, are destroyed daily, yet the elimination of iron in the urine and

feces during iron starvation is only about 6 mg., and the average daily diet supplies only about 8 to 10 mg. The iron compounds liberated in the body appear to be used over and over again in the construction of new blood pigment. A prolonged restriction of iron in the diet may, however, impair the formation of hemoglobin and thus lead to anemia. Additional iron is particularly required when anemia has resulted from hemorrhage. It has been shown by a number of investigators that when anemia is produced in animals by bleeding, recovery is more rapid and more perfect if iron be given than if iron be withheld. If, however, anemia results from a toxic destruction of the red cells, the iron in the body is not necessarily depleted, and, in such cases, the addition of iron to the diet is usually without effect.

Lipoids

Even though mixtures of pure fats, carbohydrates, proteins and properly balanced salts are fed to growing animals in quantities sufficient to supply their requirements, disturbances in growth and nutrition develop sooner or later. McCollum and Davis fed growing rats on balanced salt mixtures, casein, lard and carbohydrates. For 70 to 120 days these animals

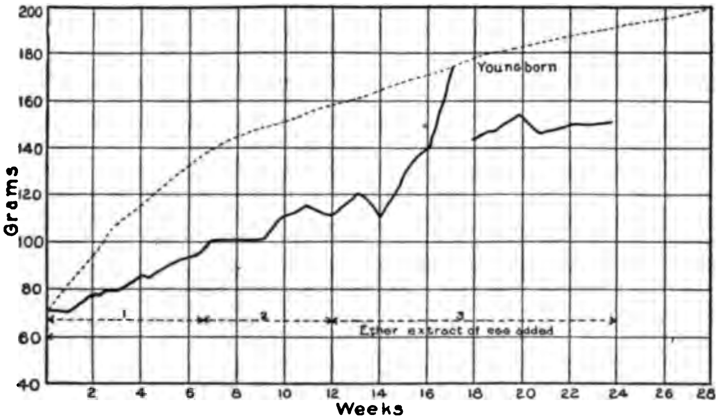


Fig. 66.—The Necessity of Certain Lipins for Normal Growth. The Dotted Line Represents the Normal Growth Line for the Rat. The Lower Line Represents the Growth of a Rat Maintained on Salt Mixtures and Purified Foods. When the Ethereal Extract from Egg Was Added to the Diet Normal Growth Was Resumed and the Animal Bore Young. (From McCollum and Davis, Jour. Biol. Chem.)

grew in a fairly normal manner. Beyond this time, however, growth ceased, although the animals might remain in apparent health for some time longer and females bore offspring while on this diet (Fig. 66). None of the mothers, however, were able to produce enough milk to nourish their offspring.

Certain Lipoids Essential to Growth.—If rats that had ceased to grow on the above diet were given the ether extract of egg or of butter,

growth was resumed in a normal manner. Evidently some substance is present in these ethereal extracts which is essential for growth. That it is not a fat or an oil, in the ordinary sense, is indicated by the fact that lard, olive oil and almond oil proved ineffective; whereas butter fat, cod liver oil, and the ethereal extract of egg yolk furnished the requisite element that led to a continuance of growth. The nature of this ethereal extract is not known, but it is evident that certain lipoids which differ from the ordinary fats are requisite for growth.

Beriberi

The importance of minute quantities of an unknown substance for the proper nutrition of the body has also become evident from studies of the etiology of certain nutritional diseases, among which beriberi and scurvy are the most important. In 1897 Eykman called attention to the fact that beriberi was prevalent among those rice-eating nations which partook of rice prepared in a certain way. When the rice was eaten with its husk attached beriberi did not develop, whereas when white rice from which the husk had been completely removed by the process of polishing was the exclusive article of diet beriberi invariably developed. Eykman found, furthermore, that when chickens or pigeons were fed solely on such white rice they developed a disease characterized by polyneuritis with paralysis of the legs which is comparable to the neuritic form of beriberi in man. The addition of rice polishings to the diet of animals or of man prevented beriberi. Little has observed the occurrence of beriberi among the inhabitants of Newfoundland and Labrador, who subsist, during certain portions of the year, on a diet of white bread, molasses and tea. The substitution of whole wheat flour for white flour prevented the disease. Experimental polyneuritis may be induced in fowls by an exclusive white bread diet, whereas it does not occur if whole wheat bread be fed (Ohler). The conditions here are evidently analogous to those that pertain to rice. The outer portion of the wheat grain, like the outer portion of rice, contains a substance which has the property of preventing the development of a polyneuritis in man and animals.

The exact nature of this substance is not known. It is soluble in water and alcohol and is dialyzable. Apparently it is free of phosphorus and of sulphur and consists of a complex nitrogen containing substances related to the pyramidin bases (Funk). Heating to 120° F. destroys it.

Scurvy

It has long been known that scurvy is due to an improper diet, and particularly to the prolonged consumption of a diet consisting of preserved food and cereals. The addition of lime juice, of fresh vegetables or of fruits to the diet prevents and cures scurvy. The experience of arctic

explorers has also emphasized the fact that an abundance of fresh meat is an effective antiscorbutic. Holst and Fröhlich showed that scurvy could be produced experimentally by feeding rabbits and guinea-pigs exclusively on oats, barley, bread, and rice, and that it could be prevented by the addition to such diets of the antiscorbutics just enumerated.

The antiscorbutic substance apparently differs from that which prevents beriberi. It appears to be more readily destroyed by heat and by chemical manipulations. Prolonged sterilization by heat, therefore, robs a food of its antiscorbutic properties. The form of scurvy that occurs in infants appears to be favored by a diet of boiled milk, particularly when this is combined with cereals. Like that of adults it is prevented and cured by the administration of orange juice. It is interesting that Hess and Fish found that cod liver oil does not prevent the incidence of scurvy in infants, thus showing that this disease differs from that induced in animals by a lack of certain lipoids.

In conclusion we may say that, in addition to its energy and protein requirements, the body needs a variety of other substances in order to develop and maintain itself. These substances are in part known and consist of certain salts, lipoids and the antiscorbutic and anti-beriberi substances. That these comprise the entire list of substances necessary for normal development and maintenance seems, however, improbable. It is possible that rickets, pellagra, and other diseases may depend upon such nutritional defects. In the normal diet a sufficient amount of these substances is present. When the diet becomes very one-sided, however, nutritional diseases from some specific food defect are apt to appear.

Some Disturbances in the Lipoids

Lipemia

It has long been known that the blood serum, instead of being clear or slightly opalescent, may be distinctly milky, because it contains numerous fine fat particles in suspension. To this condition the name of lipemia has been given. These fine refractile particles may be seen under the microscope, especially when examined by the dark field illumination. Similar particles are seen normally, and are known as hemokonia, but their number is ordinarily not sufficiently great to produce a milky serum.

After a twelve- to eighteen-hour fast the blood is almost free of hemokonia. If now a meal, rich in fat, be taken, the number of granules in the blood rapidly increases, and reaches its maximum in from two to six hours, at which time the spaces between the red corpuscles may be swarming with hemokonia. The blood serum may indeed become distinctly milky, a veritable alimentary lipemia. According to Lemierre and his associates, the exclusion of bile from the intestinal tract prevents the appearance of these

fat particles in the peripheral blood after a fatty meal. This absence of a microscopic alimentary lipemia is attributed by these authors to the absence of bile salts rather than of bile pigments in the intestines.

The degree of milkiness, or the number of hemokonia present in the blood, roughly parallels its content of fat as determined chemically. The parallelism is not an exact one, however, and it is certain that fat is also present in the blood in an invisible state.

Pathological Lipemia.—Excessive lipemia may occur in a variety of pathological conditions. In the later stages of prolonged starvation, after the glycogen reservoirs have been reduced and the individual is living largely on his body fat, lipemia is common. In anemias and cachexias, in chronic nephritis, in diabetes mellitus, in alcoholism, and in poisoning with certain drugs, lipemia may also be unusually marked. Particularly is this true of patients suffering from severe diabetes complicated by acidosis. During coma extraordinary amounts of fatty substances, amounting to 12 to even 27 per cent of the blood, have been observed. In such cases the lipemia may even be evident on ophthalmoscopic examination by reason of the milky appearance of the retinal vessels.

Increased Mobilization of Fat.—These pathological increases in the amount of visible fat in the blood are frequently associated with the mobilization of unusual quantities of fat in the body. In the later stages of starvation, for example, the individual is deriving 80 per cent or more of his energy requirements from the fats stored in his body. In severe types of diabetes the patient is living almost entirely on fats and proteins, owing to his inability to utilize carbohydrates. Why the amount of fat in the blood should be raised to such unusual heights during conditions associated with increased fat combustion is not known: but it may be pointed out that an excess of fat in the blood would aid its combustion, because the cells are surrounded by this substance in higher concentration.

In some of the conditions enumerated above there is neither an alimentary lipemia nor an excessive combustion of fat. A normal individual can dispose of very considerable alimentary lipemias by removing the excess of fat from the blood. Possibly the cause of certain pathological types of lipemia lies in some failure to remove fat particles from the blood. The exact nature of the defect, however, is not known.

Fatty Degeneration

Fat occurs not only in the typical fat cells of the body, but also in the parenchymatous cells of the liver, spleen, kidneys, heart and other organs. Under various pathological conditions the amount of visible fat in these organs is increased. In some cases the cell contains a few relatively large droplets, and its structure and function appear to be but little disturbed. Such a condition, evidently one of fat storage, is usually designated as *fatty infiltration*. On the other hand, fat may be present in parenchyma-

tous cells as very numerous and minute particles, and this change may be associated with a certain amount of cellular distintegration and with functional changes. In phosphorus poisoning, for example, the fatty degeneration of the liver is accompanied by increased autolysis, and the fatty degeneration of the heart muscle is accompanied by a tendency to cardiac dilatation (page 16). This type of fatty change has been called *fatty degeneration.*

Cell Proteins Not Main Source.—Virchow held that fatty degeneration arose from a transformation of the cell proteins into fat. We know that proteins may be the source of carbohydrates in the body, and that carbohydrates in turn may be converted into fat, so that the possibility of a conversion of protein into fat must be admitted. Nevertheless, it is certain that the fat seen in fatty degeneration is derived for the most part from other sources than the disintegration of cell proteins.

1. Invisible Converted into Visible Fat.—Two sources for the visible fat particles in fatty degeneration have been established. In the first place, it is known that fatty substances may be present and demonstrable by chemical methods, even though fat droplets are not visible under the microscope. If for any reason these fatty substances become visible then the cells will contain microscopic fat. Such a change has been observed when organs have been removed from the body and have been allowed to digest themselves. At a certain stage of autolysis there may develop the appearance of fatty degeneration. In such cases there is no possibility that the visible fat is derived from other parts of the body. It must, therefore, have arisen either from invisible fat previously present in the tissue or from the cell proteins or other constituents. Exact chemical studies have demonstrated that the amount of fatty substances in the cells is not increased during this type of fatty degeneration. Evidently, therefore, the appearance of fatty degeneration in such cases is due to the conversion of invisible into visible fat. Such a change implies that the conditions for fat solution have changed or that organic fatty combinations have been disrupted. In either case a change in the finer chemistry of the cell has taken place.

2. Fat from other Parts.—The fatty degeneration that occurs in the intact animal may or may not be accompanied by an increased amount of fat in the cells. Thus fatty degeneration of the kidneys, the spleen, and the muscles is usually accompanied by no increase in the amount of fat as determined by chemical methods. On the other hand, the fatty liver and the fatty heart muscle may show an excessive quantity of fat. Rosenfeld has shown that the extra fat in the liver is derived from a transportation of fat from other parts of the body to the diseased organ. If animals are fed on a fat that does not normally occur in their bodies, a part of this fat is deposited without change in the fat depots, and the altered character of these deposits may be demonstrated. When such animals are later poi-

soned with phosphorus, the fat collections in the liver show a composition similar to that present elsewhere in the body. Evidently the foreign fat present in the adipose tissues has been carried to the liver. Had fat arisen in the liver itself it would not have been influenced by the composition of the storage deposit elsewhere. Furthermore, Rosenfeld has shown that if an animal has been rendered very poor in body fat, the administration of phosphorus does not produce a typical fatty liver. It follows, therefore, that fatty degeneration may be due: first, to changes which render visible the fats already in the cells; and, second, to a transportation of fats from the storage depots to the diseased organ.

Change in Finer Chemistry of Cells.—The significance of fatty degeneration can no longer be settled by the assumption that it is due to a disintegration of the cell proteins, and hence means serious cellular disease. According to Rosenfeld, indeed, fatty degeneration may be regarded as a compensatory process, whereby cells with an increased metabolism endeavor to meet their needs by accumulating fat. He believes that the cells disintegrate only when this source of energy fails to supply their needs. We know, at least, that fatty degeneration indicates some disturbance in the finer chemistry of the cells. How seriously this disturbance affects the function of the cells can be learned only by other methods of study. In phosphorus poisoning the fatty liver is associated with increased autolysis, and the fatty heart is associated with an unusual tendency to dilatation. To what extent the less marked types of fatty degeneration, such as occur not infrequently at autopsies, indicate impairment of the functional activities of the cells is not known.

Cholesterin

In addition to the ordinary fats, the body contains a number of other substances which are related to the fats in that they are soluble in ordinary fat solvent. These substances, called lipoids, have been mentioned earlier in the chapter. Among the more important of the lipoids are cholesterin and lecithin. Within the past few years a number of relatively simple methods for determining the quantity of cholesterin in the body tissues and fluids have been developed, and these have made it possible to study the quantity of this substance in various pathological conditions. The greater part of the cholesterin in the body is present in combination with fatty acids, and this combination must be broken up in order to determine the total cholesterin present. Only in the bile is the greater part of the cholesterin in a free condition.

Cholesterinemia

The total amount of cholesterin in the blood serum of normal individuals varies within rather narrow limits, the average amount being about

0.15-0.18 per cent. After feeding with cholesterin or with cholesterin-containing foods, such as egg yolk, the percentage in the blood is increased. A physiological hypercholesterinemia also occurs during the later months of pregnancy.

Among the pathological causes of hypercholesterinemia is a complete occlusion of the common bile duct. Since cholesterin is excreted in the bile, it would appear that its increase in the body fluids during the biliary obstruction was a result of retention. This view is supported by the observations of Widal, Weil and Laudet, who found that in this type of cholesterinemia an unusual proportion of free cholesterin, such as occurs in bile, is present in the blood. Cholesterin is also increased in the blood in lipemia, in severe cases of diabetes, in nephritis and in related conditions (arteriosclerosis). In some of these conditions the hypercholesterinemia appears to be associated with a mobilization of other fatty substances in the body.

Local Cholesterin Deposits

A local increase in the amount of cholesterin occurs in sclerotic blood vessels, in the white plaques of nephritis retinitis, in the arcus senilis, in xanthomata, in old infarcts, in the caseous material of tuberculous lesions and in the cholesteatomatous tumors of the ear and cranial cavity. The majority of gall-stones consists largely of cholesterin and certain stones are composed almost entirely of this substance.

In many of these cases the local deposits depend doubtlessly upon local changes in the tissues, which in some manner favor a deposit of cholesterin. In tuberculosis, for example, the amount of cholesterin in the blood is usually normal or diminished, and its deposition in caseous material must be due to local changes. On the other hand, certain cholesterin deposits are frequently associated with an increased percentage in the blood, and it is possible that the deposit depends in part upon this increase. Multiple tuberous xanthomata, for example, which are composed largely of cholesterin deposits, are usually associated with hypercholesterinemia. They occur most frequently in jaundice and diabetes, conditions in which the cholesterin of the blood is usually increased. The relation between pregnancy and gall-stones may depend in part upon the fact that hypercholesterinemia is almost regularly observed during the later months of pregnancy. To what extent the cholesterin deposits in atheromatous arteries, in nephritic retinitis and in the arcus senilis depend upon the increased amount of this substance, that is present at times in the blood of these patients, is not known. The possible relation is emphasized by the experiments of Anitschkou, who found that when cholesterin was fed to rabbits arterial changes developed.

Acidosis

Formation of Acids in the Body

During metabolism acids are constantly being formed. The carbon present in proteins, fats and carbohydrates is mostly burned to carbonic acid; the sulphur contained in proteins is in part converted into sulphuric acid, while the phosphorus derived from nucleoproteins and from lecithin is converted into phosphoric acid. In addition, various organic acids arise during the intermediary metabolism. Thus fatty acids are set free from fat, and the deaminization of amino acids leaves behind an organic acid from which the alkaline amino radicle has been removed. Glucose may, under certain cicumstances, give rise to lactic acid. If these organic acids that are formed during the intermediary metabolism fail to burn to their normal end products—i. e., to water and carbon dioxid—they increase the amount of acid that must leave the body by way of the kidneys.

The formation of aceto-acetic and beta-oxybutyric acids will be discussed in the chapter on Diabetes under the section devoted to the acetone bodies.

Lactic Acid

Particular interest is attached to the occurrence of lactic acid in the body. It is well known that when an isolated voluntary muscle is made to contract it becomes more acid, and that this is due mainly to the formation of a dextrorotatory lactic acid (sarcolactic acid). When muscles or other tissues die they become acid for a similar reason.

Embden and his associates sought to determine the derivation of lactic acid by perfusing fluids through the liver. In this way they showed that lactic acid could be formed from glycogen stored in the liver or from glucose or alanin added to the perfusion fluid. It is probable, therefore, that lactic acid may arise in the intermediary metabolism either from carbohydrates or from certain of the protein-building stones. Apparently it may also originate from other less understood substances. Among the conditions which favor the formation of lactic acid is a lack of oxygen. Indeed, Woodyatt believes that the combustion of glucose does not normally pass through a lactic acid stage, but that this acid arises only when there is diminished oxidation.

Urine.—Small amounts of lactic acid have been isolated from the body fluids and from various organs. When the amount present in the blood is increased, lactic acid passes into the urine. Thus, after violent muscular exercise, it has been found both in the urine and in increased amounts in the blood. During very violent muscular exercise the supply of oxygen to the muscles may become insufficient for their increased needs,

despite the marked increase in the respiratory exchange. The elimination of lactic acid after convulsive seizures of various kinds is probably to be attributed to the violent muscular contractions. During severe asphyxia the amount of lactic acid in the blood may also be increased owing to the lack of oxygen. In carbon monoxid poisoning, with a marked reduction in the oxygen-carrying capacity of the hemoglobin, the same is true. The lactic acid which appears in the urine in association with severe hepatic degenerations, such as occur in phosphorus poisoning, appears to be due to some inability on the part of the cells to utilize the oxygen supplied to them.

The Neutrality of the Blood

Despite the constant formation of acid substances in the body, and despite numerous variations in the amount of acid- or alkali-forming substances taken in the food, the reaction of the blood remains practically constant under normal as well as under pathological conditions. This reaction is so slightly alkaline that it may be regarded as almost neutral. The mechanism whereby this neutrality is maintained despite variations in acid or alkali intake, and despite the normal and pathological formation of acids within the body, depends upon at least three factors: (1) the composition of the salts in the blood; (2) the elimination of acids through the lungs and kidneys; and (3) the neutralization of acids by an increase in ammonia.

(1) The Blood Salts

L. J. Henderson has pointed out that mixtures of carbonic acid, carbonates and phosphates, such as occur in the blood, possess the property of maintaining an almost constant and slightly alkaline reaction despite the addition of considerable quantities of either acids or alkalis.

(2) Elimination of Acids

The neutrality of the blood is also maintained by variations in the elimination of acid substances from the body. Carbon dioxid is given off from the lungs and an acid urine is secreted by the kidneys. Both serve to regulate the chemical reaction of the body. When acid-forming substances are taken by mouth, the urine, within limits, becomes more acid; whereas when alkalis are taken the urine becomes more alkaline. The content of carbonic acid in the blood is influenced by the amount of other acids present. The respiratory center is exceedingly sensitive to changes in the acidity of the blood that comes to it. When for any reason this acidity is even slightly increased, the center is stimulated, the respirations are increased, the tension of carbon dioxid in the pulmonary alveoli is

diminished and more carbon dioxid is given off from the blood. This reduction of carbonic acid in the blood continues until the reaction of this fluid approximates the normal. In this way any excess of other acids in the blood is compensated for by a reduction of carbonic acid (see Respiration).

(3) Increased Ammonia Formation

It is obvious that, if the fixed bases (sodium, potassium, calcium, magnesium, etc.) were utilized by the body for the neutralization of excess acid, a continuous loss of such bases through the kidney would ultimately cause an impoverishment of the body in these substances; unless, indeed, the supply in the food were correspondingly increased. Of great importance, therefore, is the fact that the body has at its disposal a variable quantity of alkali in the form of ammonia. Ordinarily the ammonia that is split off from the amino acids is for the most part converted into urea and is eliminated in that form (page 235). When there is an excessive amount of acid in the body, however, a part of the ammonia, instead of being converted into urea, unites with the acid and is excreted in the urine as ammonium salts.

The quantity of ammonia which is available for this purpose depends largely upon the amount of protein catabolism. In general, carnivora withstand the administration of acid by mouth better than herbivora, because a larger amount of nitrogenous waste is available for ammonia formation. If carnivora be given a diet low in proteins, or if proteins be added to the diet of herbivora, the difference in resistance to acid administration disappears.

Protection of Fixed Alkalis.—This neutralization of excessive acid by ammonia tends to protect the body against a loss of its fixed alkalis. The protection is not a perfect one, however. In the earlier stages of acid administration the more available fixed alkalis are swept out of the system, and if the formation of ammonia becomes insufficient further losses occur. Under any circumstances it is probable that some loss of fixed bases always occurs, and that in the long run this may mean a serious depletion of the body.

Definition of Acidosis

It is evident from what has been said that in acidosis no marked change in the chemical reaction of the blood ordinarily occurs. It is possible that after severe damage a local production of acid may cause an acid reaction limited to a small region, but this never extends to the entire body. Indeed, an acid reaction of the blood appears to be incompatible with life, and it has only been observed occasionally as an agonal condition. By acidosis, therefore, we do not mean that the reaction of

the blood has changed to any appreciable extent, but that excessive amounts of acid radicles other than carbonic acid are present in the body.

Evidences of Acidosis

The condition of acidosis may be recognized: (1) by changes in the blood; (2) by changes in the respiration; and (3) by changes in the urine.

(1) The Blood

Of these changes those in the blood furnish the most direct and the most convincing evidence of acidosis, but the demonstration of these changes requires a relatively difficult technic. Although the reaction of the blood in the body is not changed in acidosis, there is a shifting in the relation between the amount of carbon dioxid and the amount of other acid radicles. The former is diminished while the latter is increased. If the blood, after being drawn, be saturated with carbon dioxid up to a given tension, then the excess of the other acid radicles becomes demonstrable. The hydrogen ion concentration, as determined by physicochemical methods, is increased and the saturation of hemoglobin with oxygen at certain tensions of oxygen is changed, just as it is when acid (lactic) is added to the blood (page 361). Sellards has shown also that an increase in the content of non-volatile acid in the blood may be recognized by treating the serum with alcohol, filtering and titrating the resulting filtrate with phenolphthalein before and after drying.

(2) Respiratory Changes

We have seen that a very slight increase in the acidity of the blood stimulates the respiratory center, and that as a result of this stimulation the pulmonary ventilation is increased and the tension of carbon dioxid in the pulmonary alveoli is diminished. Determinations of the tension of carbon dioxid in the pulmonary alveoli, therefore, furnish evidence as to the activity of the respiratory center and thus, indirectly, as to the amount of incombustible acid in the body. It should be noted, however, that local changes in the respiratory center, such as local asphyxia or increased irritability, may also cause a reduction in the tension of carbon dioxid in the pulmonary alveoli.

(3) The Urine

Non-volatile acids leave the body by way of the urine, and in certain cases they may be detected and estimated in this excretion. In diabetic acidosis, for example, the amount of aceto-acetic and beta-oxybutyric acids in the urine is, with certain limitations, a measure of the quantity of these acids formed in the body.

Ammonia Exertion.—Evidence of the degree of acidosis may also be obtained by determining the quantity of ammonia in the urine, for the excess of acid is in part neutralized by ammonia that would otherwise be excreted as urea. As a rule an increased excretion of ammonia in the urine is indicative of acidosis. The theoretic possibility that such an increase may be due to a primary failure to convert ammonium salts into urea has not been satisfactorily demonstrated. On the other hand, it should be remembered that when fixed alkalis, such as sodium bicarbonate, are taken by mouth, these may also serve to neutralize excesses of acid, and may cause the ammonia in the urine to be lessened or almost to disappear. Furthermore, it has been found that in severe renal disease acidosis may be present and yet the amount of ammonia may be normal or even diminished. Apparently, in these latter cases, the kidneys have lost to some extent the power to excrete ammonium salts. Similarly, in the final stages of diabetic acidosis, the excretion of the abnormal acids may not keep pace with their formation in the body, so that urinary examinations fail to indicate the degree of acidosis.

Alkali Tolerance.—The excretion of an acid urine from an alkaline blood is a normal method of eliminating acid from the body. If incombustible acids be taken by mouth, the acidity of the urine is, within limits, increased, and if fixed alkalis (sodium bicarbonate) be taken, the acidity of the urine diminishes, and it eventually becomes alkaline. When four to five grams of sodium bicarbonate are taken by mouth by a normal individual the urine usually becomes alkaline for several hours. In certain pathological conditions, little or no reduction in the acidity of the urine follows the administration of this amount of sodium bicarbonate; while in conditions of pronounced acidosis extraordinary quantities of alkali must be given before the urine becomes alkaline. According to Palmer and Henderson, the failure to produce an alkaline urine by the administration of four grams of sodium bicarbonate indicates a need on the part of the body for alkali. It is evidence of an acidosis, and the amount of alkali that must be administered in order to cause an alkaline urine may be used as a rough measure of the degree of this acidosis.

Symptoms of Acidosis

The occurrence of acidosis and its relation to clinical pictures will be discussed in some detail in the chapters on Diabetes, Respiration, and Renal Disease. It may be pointed out here, however, that an increase in the total pulmonary ventilation necessarily results from the effort on the part of the body to keep down the level of carbon dioxid in the blood. This is the direct cause of the "air-hunger" characteristic of diabetic coma. It also plays a part in the pathogenesis of certain forms of renal dyspnea.

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Chapter IV

Disturbances in the Carbohydrate Metabolism

Diabetes

General Considerations

The maintenance of a nearly uniform concentration of sugar in the circulating blood is a fundamental adjustment of the human body. In spite of variations in the amount of carbohydrates supplied to and consumed by the body, the percentage of sugar in the blood changes but slightly. In man, this percentage, as determined by reduction tests, normally varies from 0.07 to 0.11 per cent with an average of approximately 0.09 per cent. The major portion of this reduction is due to the presence of grape sugar or glucose. In addition to this relatively free or "immediate" sugar, Lépine also speaks of the "virtual" blood sugar which becomes free under special circumstances, as by exposing blood to the action of ferments or by boiling it with mineral acids, particularly hydrofluoric acid. The significance of this "virtual" blood sugar is not certain and in most studies its presence is disregarded.

Normal Carbohydrate Metabolism.—In the normal course of carbohydrate digestion, glucose and other monosaccharids are formed in the alimentary tract. These are absorbed mainly by the intestinal radicles of the portal vein and are carried by the blood stream to the liver. Excessive amounts of glucose in the portal blood are converted in part into liver glycogen, in part they are removed from the circulating blood by other less understood agencies. Other monosaccharids, and particularly levulose and galactose, are removed from the blood to a relatively large extent by the liver. These mechanisms for the removal of sugar from the circulating blood are so perfect, that even after a meal rich in carbohydrates the total blood sugar is increased by small amounts only. Thus Tachau found in nineteen individuals that the average percentage of 0.078 during fasting was increased to an average of 0.086 per cent after the adminis-

tration of 100 grams of glucose; Leire found that after giving oatmeal gruel and milk to three individuals the average percentage of blood sugar rose from 0.09 to 0.11, and Strouse found rises from an average of 0.066 before to 0.10 after ordinary meals. The glycogen which is stored in the liver is in turn gradually transformed into blood glucose to meet the body needs. These transformations of simple sugars into glycogen and of glycogen into glucose are performed by special hepatic ferments. The chemical reactions are, broadly speaking, those of dehydration and polymerization or the reverse and they may be represented by the following formula:

$$\underset{\text{Glucose}}{n\ C_6H_{12}O_6} \rightleftarrows n\ \underset{\text{Water}}{H_2O} + \underset{\text{Glycogen}}{C_{6n}H_{10n}O_{5n}}$$

The liver acts as the chief primary storage reservoir for carbohydrates coming from the digestive tract, and it is one of the most important organs serving to prevent rapid fluctuations in the blood sugar. In this regulation of the percentage of sugar in the circulating blood it is assisted by other agencies, among which are the deposition of glycogen in other tissues, especially the muscles, and the formation of fat from glucose. These deposits of glycogen in other tissues and of fat represent a secondary system of storage for excess energy-containing material, and they assist the liver in removing excesses of sugar from the circulating blood. The importance of other organs in this action is suggested: (1) by the experiments of Bang who found relatively small increases in the liver glycogen of rabbits after the administration of glucose; (2) by the relatively slight increase in the blood sugar after feeding glucose to dogs with the Eck fistula (Michaud); and (3) by the failure to find alimentary glycosuria after feeding glucose to patients with liver disease.

Combustion of Glucose.—The combustion of glucose occurs mainly in the muscles and the completed reaction is represented by the formula:

$$\underset{\text{Glucose}}{C_6H_{12}O_6} + \underset{\text{Oxygen}}{6O_2} = 6\ \underset{\text{Water}}{H_2O} + 6\ \underset{\text{Carbon dioxide}}{CO_2}$$

In the burning of a single molecule of glucose six molecules of oxygen are used and six molecules of carbon dioxid are formed. The ratio of the former to the latter is 1.0, and if glucose were the only substance burned in the body the ratio of the amount of oxygen absorbed and of carbon dioxid given off by the lungs, i. e., the respiratory quotient, would be 1.0. Little is known about the intermediary steps through which the sugar passes during the process of combustion, but lactic acid is generally regarded as an intermediary product. A. E. Taylor has suggested the following as a possible series of transformations:

$$
\begin{array}{llll}
\mathrm{CHO} & \mathrm{COH} & \mathrm{COOH} & \\
| & | & | & \\
\mathrm{CHOH} & \mathrm{CO} & \mathrm{CHOH} & \mathrm{C_2H_5OH+CO_2} \\
| & | & | & \\
\mathrm{CHOH} & \mathrm{CH_3} & \mathrm{CH_3} & \\
| & \overline{} & \overline{} & \\
\mathrm{CHOH} & \mathrm{COH} & \mathrm{COOH} & \mathrm{C_2H_5OH+CO_2} \\
| & | & | & \\
\mathrm{CHOH} & \mathrm{CO} & \mathrm{CHOH} & \\
| & | & | & \\
\mathrm{CH_2OH} & \mathrm{CH_3} & \mathrm{CH_3} & \\
\text{Glucose} & \text{Methylglyoxal} & \text{Lactic Acid} & \text{Alcohol} \quad \text{Carbon Dioxid}
\end{array}
$$

Under normal conditions the kidneys allow only minimal quantities of sugar to pass through them into the urine.

Pathological Disturbances.—Pathological disturbances in the carbohydrate metabolism of the body may depend upon various factors. Of these we may mention an abnormal conversion of stored glycogen into blood glucose, an insufficient removal from the circulating blood of the glucose or other monosaccharids absorbed from the intestines, an insufficient combustion of glucose, and an abnormal permeability of the kidneys which allows glucose to pass into the urine with unusual ease. It is the purpose of pathological studies to determine, so far as possible, the exact portion of the carbohydrate mechanism which is at fault in producing abnormal glucemias or glycosurias.

Renal Glycosurias

In spite of the considerable amount of sugar in the blood, only very minute quantities normally pass through the kidneys into the urine. In other words, normal kidneys are nearly impermeable to the concentration of glucose present in normal blood.

Cause of Renal Impermeability to Glucose.—The cause of this renal impermeability has not been definitely established. On the one hand, it has been held that hemic glucose is in a free chemical state, and that the renal cells possess physical or chemical properties which render them impervious to such amounts as occur normally in the blood. This view finds an analogy in the fact that the secretion of sodium chlorid by the kidneys seems to depend not upon the total amount of this salt in the blood, but upon the degree to which the amount in the blood exceeds a definite limit. When the sodium chlorid content of the blood falls and this limit is approached, the elimination of sodium chlorid through the kidneys sinks to a minimum (page 429).

On the other hand, it has been suggested that the renal impermeability to the glucose is due to the latter being present in normal blood in some hypothetical colloidal combination which, like albumin, cannot readily

pass the renal filter. The possible occurrence of such glucose combinations in the blood cannot be denied, though chemical proof of their existence in such quantity as would bear out this hypothesis has not been brought. Nevertheless, various authors have inclined toward the view that glucose normally circulates in some loose chemical combination which prevents its excretion by the kidney. The evidence in favor of this view is of a biological rather than of a chemical character. It affords a plausible explanation of the impermeability of the kidneys to the normal blood sugar. Furthermore, Allen states that while intravenous injections of glucose produce diuresis, the administration by other routes checks urinary secretion. To explain this difference, he assumes that some hypothetical glucose compound is formed during the process of absorption.

Classification Based on Renal Permeability.—Whatever may be the ultimate explanation for the normal impermeability of the kidneys to the blood sugar, the current division of glycosurias is based upon this conception of a certain threshold limit of renal impermeability. On the one hand, we have those forms of glycosuria in which the renal threshold is lowered. Glycosuria occurs in spite of a normal amount of sugar in the blood. These are the so-called renal glycosurias. On the other hand, we have the commoner forms of glycosuria which are associated with a definite hyperglucemia and where the kidneys remove a portion of the excess sugar from the circulating blood. In the former case, the explanation for the glycosuria is to be sought either in changes of the renal permeability or in changes in the hypothetical glucose combination of normal blood. In the latter case, the glycosuria is due to the hyperglucemia, and attention should be directed to the causes which have increased the sugar content of the blood rather than to its renal excretion.

The relation of the kidneys to blood sugar has frequently been likened to that of a dam which impounds a lake of water. So long as the water level remains below that of the dam, none flows over. An overflow may be produced on the one hand by a lowering of the dam (renal glycosuria) and on the other hand by a rise in the level of the water (hyperglucemia). This analogy cannot be pushed too far, however, for undoubtedly the conditions in the animal body are far more complex than in the mechanical restraint exercised by a dam upon a lake of water. The level of renal impermeability appears to be a variable quantity even in a given individual. As a rule, sugar appears in the urine when its concentration in the blood reaches 0.16 per cent, but the threshold limit may vary from 0.12 to 0.18 without being distinctly pathological.

Phlorhizin Glycosuria

In 1886, von Mering showed that the administration of the glucosid, phlorhizin, to animals was followed by the appearance of dextrose in the

urine. The amount of urinary sugar excreted may be far in excess of that contained in the glucosid itself and, furthermore, a large part of the phlorhizin injected may subsequently be recovered from the urine. It is evident that most, if not all, of the sugar in the urine is derived from the poisoned animal and not from the drug. The glycosuria which follows the administration of phlorhizin is not associated with hyperglucemia. Indeed the concentration of glucose in the blood is often lowered. Thus, repeated injections given by Frank and Isaac to fasting dogs reduced the blood sugar to 0.05, 0.03 and even to 0.012 per cent. Phlorhizin glycosuria, therefore, belongs to the class of so-called renal glycosurias.

Phlorhizin Acts on Renal Tubules.—All our evidence indicates that the renal tubules constitute the portion of the kidneys acted upon by phlorhizin. In the frog, the glomeruli receive a different blood supply from the tubules, and Mosberg has shown that when the glomerular vessels of these animals are ligated, injections of phlorhizin still produces glycosuria, while injections of glucose now fail to do so. In these animals, the urinary glucose following an excess of blood sugar is excreted through the glomeruli, while the urinary glucose after phlorhizin injection passes through the tubules. By histochemical studies Seelig has shown that after giving phlorhizin to rabbits sugar can be demonstrated in and between the tubules, while it is present only in very small amounts in the glomeruli. Chemical analyses by Nishi have shown that in contrast to the normal kidney and to other forms of glycosuria, the kidney of phlorhizin poisoning shows a relatively large amount of sugar in the medulla. Various anatomical studies on phlorhizin kidneys have also shown that the principal anatomical lesions are located in the tubules. Finally injections of certain dyes, such as carmin and methylene blue, which are excreted through the tubules, may inhibit the action of subsequent phlorhizin injections.

Effects of Phlorhizin Poisoning.—The essential disturbances of carbohydrate metabolism produced by the administration of phlorhizin appears to be a drainage of blood glucose out through the kidneys. The other effects, largely secondary, are interesting and instructive, and as they have served to throw much light upon the problems of diabetes, they will be referred to frequently in the discussion of that disease. The drainage of glucose from the blood is followed by a reduction in the amount of glycogen stored in the liver, and to a lesser extent by a reduction in the amount of muscle glycogen. Yet the glycogen does not entirely disappear from the liver even though the animal is fasting, and it rapidly reaccumulates when the administration of phlorhizin is discontinued. Lusk showed that when an animal is given sufficiently large doses of phlorhizin at sufficiently frequent intervals, all of the sugar derived from the diet and all that is formed within the body may be completely elim-

inated by the kidneys. The inability of the completely phlorhizinized animal to burn dextrose is apparently due to a low concentration of sugar in the body, for if large quantities of carbohydrates are given, so as to maintain a higher concentration of sugar in the body, considerable amounts may be utilized. If large amounts of carbohydrates are not furnished, the caloric requirements of the animal are met by an increased metabolism of body proteins, and in dogs the urinary nitrogen may equal five times that of the control fasting animals (Reilly, Nolan and Lusk). Finally acetone bodies may appear in the urine and the animal may pass into a condition resembling diabetic coma. In phlorhizin poisoning, therefore, we have a very severe disturbance in the carbohydrate metabolism of the body, due primarily to an increased permeability of the renal filter to the blood glucose and to a consequent drainage of glucose from the body. Whether this drainage through the kidney is due primarily to changes in the renal filter itself, or to changes in some hypothetical combination of the blood sugar which allows it to pass a normal kidney, has not been definitely established. The present tendency, however, is to locate the essential changes in the kidney rather than in the blood (Lusk, Frank).

Other Renal Glycosurias

Much attention has been devoted to the possible existence of other glycosurias analogous to that produced by phlorhizin; where, in spite of a normal glucemia, there is a passage of glucose into the urine. Such conditions are spoken of as renal glycosurias or, where they are chronic, as renal diabetes. While such conditions have been proved to exist both experimentally and clinically, we know of none that are comparable in severity with that produced by phlorhizin poisoning. Indeed the latter represents the most severe type of glycosuria that can be produced experimentally, even exceeding in severity the glycosuria which follows total removal of the pancreas. As compared with the latter, the amount of sugar excreted during starvation is greater, the proportion of sugar derived from proteins is greater, the protein destruction is greater, and acidosis can be more regularly produced.

Experimentally it has been found that certain kidney poisons, and in particular corrosive sublimate, uranium salts, and the chromates, will induce mild degrees of glycosuria without appreciable increases in blood sugar (Frank). These salts produce specific changes in the renal tubules and the glycosuria is evidently renal in character. Certain organ extracts and certain sera have a similar action. The mechanism of salt glycosuria is less certain, but here also there seems to be some reduction in the renal permeability to glucose.

Renal Glycosurias in Man

The question as to the occurrence of renal glycosurias in man was opened by Lépine and by Klemperer. The case described by the latter, however, has not withstood later criticism, and the same might be said of several cases subsequently reported. In 1913, Frank was able to collect from the literature only six cases which he regarded as renal glycosurias, and to these he added two new observations. Still more recently it has been shown by Mann, as well as by Novak, Porges and Strisower, that the glycosuria of pregnancy, which is by no means infrequent and which has long been known for its benign character, is unassociated with any increase in the glucose of the blood. It therefore conforms to the principal criteria of a renal glycosuria, and up to the present time it is the commonest type of this affection known to occur in man. Quite recently, also, E. Frank has described cases of renal glycosuria in adolescent individuals.

Clinical Manifestations.—The cases of renal glycosuria thus far described in man have been of a very mild character. The amount of sugar in the urine has varied from mere traces to 1.5 per cent or slightly more. A surprising lack of relationship between the amount of sugar in the urine and the character of the diet is characteristic of this affection. While there is a tendency to an increased excretion of sugar by the kidneys with any increased intake of carbohydrates and vice versa, the relation to diet is never so striking as it is in correspondingly mild cases of true diabetes mellitus. The excretion of sugar may even continue after all carbohydrates have been eliminated from the diet. Renal glycosuria may, therefore, be suspected when a mild glycosuria does not disappear promptly after the patient is placed on a carbohydrate free diet or when unaccountable variations occur in the excretion of sugar. To demonstrate a renal glycosuria, however, it is necessary to find a normal quantity of glucose in the blood at a time when sugar is appearing in the urine. Other evidences of kidney disease may be present or absent. In practice, the recognition of the occasional occurrence of a renal glycosuria is important, because of the relatively favorable prognosis of this condition, and because in such patients there is not the same necessity for dieting as in the milder types of true diabetes mellitus.

Alimentary Glycosuria and Related Conditions

Alimentary Glycosuria

The glucose taken in the diet, together with that formed during the digestion of other carbohydrates, is for the most part carried to the liver in the portal blood. Here a part of the excess of glucose is converted into

glycogen. Apparently another part is rapidly removed from the blood in other tissues, for Michaud has shown that when the blood is shunted from the vena porta to the inferior vena cava by an Eck fistula the giving of 100 grams of glucose to a dog does not raise the blood sugar excessively, and Bang failed to find sufficient amounts of glycogen in the liver or of glucose in the blood to account for the amounts absorbed after giving glucose to fasting rabbits (also after intravenous injections). By these means, any marked rise in the concentration of sugar in the general circulation after meals is prevented. As sugar ceases to come from the alimentary tract and as that in the blood is consumed, a part of the hepatic glycogen is reconverted into glucose and again enters the blood stream. Since the human liver has a storage capacity of 150 to 200 grams of glycogen, it is evident that it is able to arrest and fix any ordinary amount of glucose coming from the intestinal tract, provided it is permitted to discharge some of its contents between meals, and provided that the sugar from the digestive tract is not absorbed too rapidly.

Overrapid Absorption of Glucose.—Under special circumstances, however, the glucose absorbed from the alimentary tract is not removed from the circulating blood with sufficient speed to prevent a general hyperglucemia which is sufficient to cause an elimination of glucose through the kidneys. Normal individuals may usually ingest large quantities of starchy foods with their meals without causing glycosuria. Owing to the time consumed in digestion and absorption, the liver and other organs are given time to remove most of the excess of glucose from the circulating blood and so prevent a marked hyperglucemia. Under certain conditions, however, the absorption of glucose is so rapid that the mechanism for its removal from the circulating blood is insufficient to prevent a rise in the level of blood sugar sufficient to cause glycosuria. This type of glycosuria is spoken of as an alimentary glycosuria. It was formerly believed that while normal individuals might show alimentary glycosuria after taking excessive quantities of sugar, they could take unlimited quantities of starch by mouth without the appearance of sugar in the urine. Occasionally, however, a rapid digestion of large quantities of starch may lead to alimentary glycosuria.

Alimentary Tolerance.—The maximum amount of sugar that may be taken by mouth without the appearance of glycosuria is usually spoken of as the alimentary tolerance or assimilative capacity for glucose. This tolerance varies with different individuals and with the same individual under different conditions. In normal individuals 100 grams of glucose may usually be taken by mouth in one dose without the appearance of a glycosuria (Strauss, Oordt, etc.), and larger amounts up to and above 300 grams have been tolerated (Hofmeister and Bezzler). The tolerance varies with the age of the individual. Elderly persons are believed to have a somewhat lower glucose tolerance than those in youth or middle

life (von Adlor, Ehrenberg and Yitemann). According to Greenfield, the tolerance in infants and children up to the age of 10 years is also reduced. His results are shown in the following chart:

TOLERANCE

Average Age	Dextrose per Kilo
2½ years	0.4
3¼ years	1.0
4⅓ years	0.7
5⅚ years	1.4
8 years	2.1
9 years	2.8

When glucose is given to a fasting individual the tolerance is in general lower than when given with a full meal, owing to the slower rate of absorption in the latter condition.

Diminution of Tolerance.—The tolerance for glucose administered by mouth tends to be diminished in various pathological conditions. Numerous studies have been made on patients in the hope of finding a diagnostic use for reduced glucose tolerance or in the hope of throwing light upon the problems of glycosuria in general. These studies have shown that alimentary glycosuria is not a constant finding in any well-defined pathological condition. Furthermore, since its production depends upon such various factors as the rate at which the stomach discharges its contents, the rate of absorption from the intestines, the removal of excess glucose from the blood and the renal permeability, its theoretic interpretation is subject to many sources of error.

FROM ALCOHOLISM AND ACUTE INFECTIONS.—Alcoholism frequently reduces the alimentary tolerance for glucose. This reduction is more apt to occur after drinking beer than after drinking distilled liquors. Arndt, Strauss and others found that acute alcoholic intoxication and alcoholic delirium markedly reduce the tolerance for glucose but that in most cases abstinence from alcohol is followed by a rapid rise in the tolerance. Lievin found an alimentary glycosuria in 80 per cent of chronic alcoholics as compared with its occurrence in 25 per cent of normal individuals under similar test conditions. Traumata in general increase the tendency to alimentary glycosuria, but as a rule this passes off in four to ten days. Acute infections, and particularly lobar pneumonia, reduce the alimentary tolerance for glucose. Thus Poll obtained alimentary glycosuria in eleven of thirteen cases of lobar pneumonia, J. Strauss in all of eight cases, and Bleiweiss in three of seven cases. Tuberculosis does not seem to predispose to this condition.

NO DEFINITE RELATION TO ANATOMICAL DISEASE OF LIVER.—No definite relation has been established between anatomical disease of the liver and diminished tolerance to glucose. This is remarkable on account of the important rôle played by the liver in normal carbohydrate metabolism.

Either the liver does not lose this function readily, or, as seems equally probable, other organs play an important part in the immediate removal of excess glucose from the circulating blood.

In Other Conditions.—In exophthalmic goiter alimentary glycosuria is common. Kraus and Ludwig found it even when the pulse rate was not increased, Chvostek found it in 69 per cent, Goldsmith in 19 per cent and Strauss in 16 per cent of the cases investigated. It seems to be more common in the acute cases and relatively uncommon in the chronic cases. In pregnancy alimentary glycosuria is common. It is also relatively frequent in obese individuals.

Factors Influencing Alimentary Glycosuria.—It is evident from these data that alimentary glycosuria bears no constant relation to any well-defined pathological condition, and that it is not of great value as a diagnostic aid. Furthermore, it depends upon such variable factors as to render its interpretation one of great difficulty. These factors are: (1) the rapidity of absorption from the intestinal tract; (2) the ability on the part of the body to remove an excess of glucose from the circulating blood; and (3) the threshold limit at which the kidneys begin to excrete the excess into the urine. The importance of the renal threshold is shown in the lowering during pregnancy, so that rises in the concentration of blood sugar which would be without effect upon the urine of normal individuals lead to glycosuria in pregnancy (Mann). The rapidity of absorption is a factor which can never be accurately estimated, so long as the sugar is taken by mouth. Other methods of administration may eliminate this uncertainty. Thus Allen has recommended subcutaneous injections as being a more accurate test of the ability to remove glucose from the blood and Woodyatt, Sansum and Wilder have shown that continuous intravenous injections of glucose, up to 0.9 gram per kilo per hour may be given to normal individuals without provoking glycosuria.

Alimentary Glycosuria and Incipient Diabetes mellitus.—Much interest attaches itself to the relationship between alimentary glycosuria, on the one hand, and incipient diabetes mellitus, on the other. If glycosuria follows the administration of 100 grams of glucose by mouth, does it indicate that the individual has or is likely to develop diabetes mellitus? In general it may be said that the likelihood is not great, for experience has shown that alimentary glycosuria is not regularly followed by the development of diabetes mellitus. Nevertheless, a small number of patients showing alimentary glycosuria subsequently develop diabetes. One should, therefore, be suspicious of such cases, and especially so: (1) if considerable amounts of glucose, 2 per cent or over, are eliminated during the test; (2) if it is positive in conditions other than those commonly associated with alimentary glycosuria (alcoholism, hyperthyroidism, pregnancy, etc.); and (3) if it is positive in tests repeated at intervals of some months.

When the administration of 100 grams of glucose is not followed by glycosuria, can one exclude incipient diabetes mellitus? While it may be said in a general way that those who have incipient diabetes mellitus will react positively to the alimentary test, this does not seem to be an invariable rule. Mild diabetics, after having been upon a strict diet for some time, may not only have a sugar free urine, but they may be able to take considerable amounts of glucose at a single dose without the appearance of sugar in the urine. Thus Troje observed several patients, even with severe diabetes, who were able to take 100 grams of dextrose without the appearance of glucose in the urine. Kulz reports a diabetic who remained sugar free after the administration of 50 grams of glucose, and J. Strauss observed an intermittent diabetes in a patient with encephalomacia, who was able to take 200 grams of sugar without the appearance of sugar in the urine. Thus the alimentary tolerance for glucose, while of value both in the recognition and in the exclusion of incipient cases of diabetes mellitus, cannot be relied upon absolutely in either the positive or negative sense.

Alimentary Levulosuria

When levulose is absorbed from the alimentary tract it is carried to the liver and is there converted into glycogen. This has been shown by the accumulation of glycogen in the liver after feeding levulose to fasting and to depancreatized animals, as well as by perfusion experiments. The liver appears to be more essential to levulose assimilation in the body than it is to glucose assimilation, for de Filippi has demonstrated that dogs in which an Eck fistula has been established show a reduced tolerance to levulose, whereas the tolerance to glucose is little if at all affected. The same is true after removal of the liver of frogs (Sachs).

Tolerance Limit to Levulose in Man.—According to von Noorden, the usual limit of alimentary tolerance of man to levulose may be set at 120-150 grams of levulose. Recently collected statistics show that when 100 grams of levulose are administered by mouth to normal men, from ten to twenty per cent of the subjects may be expected to show levulose in the urine.

Levulosuria Test of Hepatic Function.—In certain pathological conditions of the liver, an alimentary levulosuria is relatively frequent and this test, recommended particularly by Strauss, has been extensively used as a test for hepatic function. The clinical data as to the results of the alimentary test for hepatic function are voluminous and are summarized, so far as liver disease is concerned, in the following table, which has been amplified from that given by Hohlweg, by adding the cases of Hohlweg, Goodman, Foster, von Frey, and Falk and Saxl:

ALIMENTARY LEVULOSURIA IN HEPATIC DISEASE

Disease	Positive	Negative	Per cent Positive
Cirrhosis of liver	118	19	86
Jaundice, catarrhal, cholelithiasis, etc	33	4	91
Lues of liver	11	7	61
Tumor of liver	11	19	37
Chronic passive congestion	6	32	16

When these figures are compared with the incidence of alimentary levulosuria after giving 100 grams of levulose to individuals with apparently normal livers, it is evident that in hepatic cirrhosis and in jaundice from various causes there is, as a rule, a diminished tolerance toward the alimentary ingestion of levulose. In lues and in tumors of the liver the inability to handle levulose is less pronounced, while in chronic passive congestion no marked tendency to alimentary levulosuria is present.

Alimentary Galactosuria

In 1906 Bauer introduced galactose as a functional liver test. Fischler found that dogs with an Eck fistula might excrete in the urine as much as 80 per cent of the galactose administered. Roubitschek found that alimentary galactosuria was readily produced by poisoning rabbits with phosphorus, and Bierry that it occurs in dogs poisoned with chloroform. According to von Noorden the assimilative capacity of man for the alimentary administration of galactose is 20 grams. When, however, the amount administered is in excess of this normal limit, considerable quantities of galactose pass into the urine. Bauer gave 40 grams of galactose in 400-500 c.c. of tea in the morning on an empty stomach and determined the amount of galactose eliminated during the following four or five hours. Normally not more than two grams should be eliminated under these circumstances. The following chart compiled from recent papers by Bauer, by Reiss and Jehn and by Wagner summarizes the results of this test in clinical conditions:

ALIMENTARY GALACTOSURIA

Diseases	Wagner		Reiss and Jehn		Bauer		Per cent Positive
	Cases	Positive	Cases	Positive	Cases	Positive	
Catarrhal jaundice	24	24	17	16	33	33	99
Cirrhosis of liver	10	7	15	3	32	30	70
Passive congestion	12	0	8	1	38	8	15
Cholelithiasis, etc	38	8	8	2	48	5	17
Jaundice from maglignant obstruction	..	..	5	0	..	..	
Tumors of liver	18	6	..	..	..	..	13
Metastatic carcinoma	..	..	..	..	41	0	
Primary carcinoma	..	..	..	..	2	2	
Phosphorus poisoning	..	..	..	..	2	1	
Acute yellow atrophy	..	..	..	..	1	1	..
Echinococcus liver	..	..	..	..	2	0	..
Liver abscess	..	..	..	..	3	0	..
Hematolytic jaundice	6	0	..	..	..	..	..
Pernicious anemia	3	0	..	..	..	..	..
Hyperthyroidism	14	8	..	..	..	..	..
Neuroses	10	4	..	..	..	..	..

It is seen that the tolerance after the alimentary administration of galactose is particularly lowered in catarrhal jaundice and to a lesser extent in hepatic cirrhosis. Obstructive jaundice, tumors of the liver and chronic passive congestion have but little effect upon the tolerance.

Glycosurias from Discharge of the Glycogen Reservoirs

Nervous Glycosurias

The study of glycosuria by experimental methods dates from Claude Bernard's famous puncture of the fourth ventricle. Bernard found that puncture of the space lying between the origins of the pneumogastric and auditory nerves produced both an increase in the quantity of urine and an elimination of sugar in the urine. After a successful puncture, glycosuria and polyuria generally come on within an hour and persist for several hours or occasionally for over a day. In richly nourished animals the glycosuria is more marked. Ordinarily the urine contains two or three per cent of sugar but it may contain as high as eight per cent. The presence of glycogen in the liver is a necessary prerequisite for a successful puncture, and if the liver glycogen be reduced by fasting or other methods, negative results are usually obtained. Puncture of the fourth ventricle leads to a rapid discharge of liver glycogen which produces a hyperglycemia and consequent glycosuria. In some cases, the amount of sugar excreted after the puncture has apparently been greater than the amount of glycogen stored in the liver at the time. The weight of evidence, however, supports the view that puncture of the fourth ventricle acts primarily, if not solely, upon the liver glycogen.

Increased Blood Flow Through Liver.—Following the puncture there is an increased rate of blood flow through the liver, and Bernard held that this accounted for the rapid conversion of the glycogen into blood sugar. The importance of this rapid circulation is generally recognized. Whether, in addition, changes occur in the hepatic ferments is less certain. Bang, Ljungdahl and Bohm determined the rate at which the excised rabbit's liver converted glycogen into dextrose, and they found that after puncture this rate may be twice the normal. MacLeod and Pearce, on the other hand, were unable to demonstrate that puncture increased the ferment which converts glycogen into dextrose.

Nervous Paths to the Liver.—Bernard and those following him have devoted much attention to the nervous mechanism through which the floor of the fourth ventricle acts upon the liver. Bernard found that section of the vagus nerves did not influence the glycosuria following puncture, while Eckhard showed that section of the splanchnic nerves prevented its occurrence. These facts have been confirmed by later investigators, and there is little doubt but that the effects of the punc-

ture are carried to the abdomen by way of the splanchnic nerves. Stimulation of the great splanchnic nerve causes a rise of sugar in the blood (MacLeod). The question whether puncture and splanchnic stimulation act directly upon the liver, or indirectly through a discharge of adrenal secretion, will be discussed later.

Injuries to portions of the brain other than the floor of the fourth ventricle may also be followed by glycosuria, but the effect is by no means constant or certain, except in the case of injuries in the neighborhood of the hypophysis. Stimulation of the central stump of various nerves, e. g., the vagus, has also frequently been followed by glycosuria, but MacLeod attributes this effect to the accompanying asphyxia rather than to a nervous reflex.

Glycosuria from Cerebral Disease

Clinical literature abounds with instances in which glycosuria has been associated with gross cerebral lesions (see Naunyn). These glycosurias have occurred most frequently after injuries to the head, and after cerebral hemorrhages; to a lesser extent in association with tumors, softening, systemic diseases, etc. Many of these glycosurias are transitory in character and show no tendency to pass into true diabetes mellitus. They resemble the glycosurias produced by puncture of the fourth ventricle. The anatomical lesions present have involved various portions of the brain, and the mode of action upon the medullary centers has often been obscure.

Emotional Glycosuria

Clinicians have long maintained that a relation exists between diabetes and nervous strain. Recent observations by Cannon, Folin and their coworkers have demonstrated that even in normal individuals glycosuria may be induced by violent emotions. Thus sugar has been found in the urine of students after a difficult examination and in members of a foot-ball squad which watched but did not participate in an important struggle. Possibly the high incidence of glycosuria among those admitted to hospitals for the insane is due in part to the emotions from which they suffer. Shaffer and others have pointed out that the level of blood sugar in animals is much lower when the blood is obtained by direct puncture of a vein than when the animal is subjected to pain, excitement or anesthesia, a fact which vitiates many older observations on animals.

The cause of emotional hyperglycemia and glycosuria is doubtlessly a discharge of liver glycogen induced by sympathetic nerve stimulation. It is accompanied by a simultaneous discharge of epinephrin from the adrenal gland and the latter contributes to the disturbance in carbohydrate mobilization.

Glycosuria from Disease of the Hypophysis

Particular interest attaches itself to the glycosurias which have frequently been observed in connection with injuries to or diseases in or near the hypophysis. Borchardt called attention to the frequency of glycosuria in these conditions. Rosenberger has recently analyzed the histories of 196 reported cases of acromegaly. Of these 72 patients showed a glycosuria. In seven of this group the glycosuria was transitory. In 11 others the administration of 100 grams of glucose was followed by an alimentary glycosuria. Altogether, therefore, 83, or 43 per cent, of the total showed spontaneous or alimentary glycosuria. Other patients with disease of the hypophysis tolerate unusual quantities of sugar without the occurrence of a glycosuria, and Cushing has proposed this as a functional test for the activity of the posterior lobe.

Is this tendency to glycosuria in diseases of the hypophysis due to a perversion of its internal secretion or is it to be interpreted as a manifestation of a disturbance of nervous centers in or near the gland? On this point the experimental evidence is conflicting. The injection of pituitary extracts into rabbits frequently produces glycosuria (Borchardt, Goetsch, Cushing and Jacobson), but injections into dogs do not usually produce this effect. Operations on, and injuries to, the hypophysis are frequently but not always followed by glycosuria. According to Weed, Cushing and Jacobson, stimulation of the superior cervical sympathetic ganglion and direct stimulation of the hypophysis cause a glycosuria in rabbits even after the nervous connections to the abdomen are severed, and they believe that a chemical substance is liberated from the hypophysis which discharges glycogen, independently of any nerve impulse reaching the abdominal organs. According to their view, the secretion of the hypophysis is comparable to that of the adrenal glands.

Epinephrin Glycosuria

In 1901 Blum discovered that the intravenous or subcutaneous injection of adrenal extract in various animals was followed by glycosuria, and in 1902 Herter and Richards showed that epinephrin was responsible for this action. Epinephrin glycosuria is usually associated with a hyperglycemia. After repeated injections and at times after a single intravenous injection, glycosuria fails to appear even though the blood sugar is increased to 0.25 per cent or more. Apparently the kidneys have become less permeable to blood sugar than they are normally. The permeability seems to lessen with repeated injections. If one provide for an abundant diuresis by the simultaneous injection of salt solution, the glycosuria from intravenous injections is more regularly obtained (Ritzmann).

Hyperglycemia after Epinephrin Injection.—The hyperglycemia following epinephrin injections is due to a rapid conversion of the glycogen of the body into blood sugar. In animals with rich glycogen stores a sufficiently large dose of epinephrin causes a marked diminution of the glycogen in the liver and muscles. According to Agadschanianz, the action of adrenalin upon the muscles is even more marked than upon the liver. This is noteworthy in view of the fact that puncture of the fourth ventricle acts primarily upon the liver glycogen. Glycogen appears to be the sole source of the sugar eliminated after epinephrin injections, for Ringer found that, when animals are rendered glycogen free by fasting, exposure to cold and repeated injections of phlorhizin, no increase in glycosuria results from intraperitoneal injections of epinephrin.

Relations between Epinephrin and Nervous Glycosurias.—Interesting and important relations exist between the glycosuria produced by injections of epinephrin and that following puncture of the fourth ventricle or stimulation of the splanchnic nerves. Both are temporary and both are associated with hyperglycemia due to a discharge of glycogen stored in the body. That epinephrin does not produce its effect through an action upon the nervous centers is evident from the fact that it causes glycosuria even when all nervous paths from the medulla to the abdominal cavity are severed.

On the other hand, the question has been raised whether stimulation of the medullary centers may cause glycosuria, not by a direct action upon the liver, but indirectly by increasing the secretion of epinephrin. Double epinephrectomy ordinarily prevents glycosurias after medullary puncture or stimulation of the splanchnic nerves, puncture of the fourth ventricle produces anatomical changes in the adrenal glands (Meyer, Borberg, Kahn), and the epinephrin content of the blood leaving the adrenal glands may be increased by nervous causes, and particularly by emotions and by splanchnic stimulation. It is, therefore, evident that nervous influences may increase the secretion of epinephrin, but the exact relation of this increase to nervous glycosurias is unsettled. An epinephrin injection reduces the muscle glycogen more markedly than does the puncture. Furthermore, according to Wertheimer and Battez, medullary puncture produces a heavy glycosuria in cats, even though the adrenal glands be removed; while according to MacLeod section of the hepatic plexus of nerves prevents the hyperglycemia that ordinarily follows splanchnic stimulation even though the adrenals and their nerve supply be intact.

It seems evident, therefore, that direct nervous impulses from the medulla to the liver play an important part in the pathogenesis of nervous glycosuria. At the same time, the presence of epinephrin in the blood appears to favor the production of a nervous glycosuria.

Epinephrin acts particularly upon the sympathetic nerve terminations.

Even though it play no direct part in producing the glycosurias that follow nerve stimulation, nevertheless, it may favor such glycosurias by rendering the sympathetic nerve terminations in the liver more sensitive to nervous influences.

Blood Sugar in Addison's Disease.—A regulating influence of the adrenal secretion upon the amount of blood sugar is suggested by Porges' observation that in three cases of Addison's disease the blood sugar was remarkably low. The experimental evidence bearing on this point is, however, conflicting, for while Porges as well as Bierry and Malloizel found hypoglycemia in dogs after extirpation of the adrenals, Frank and Isaac obtained negative results in rabbits until shortly before death.

Toxic Glycosurias

A large number of poisons have been found to produce glycosuria in animals. Some of these have already been mentioned. The mechanism through which many drugs act is not definitely known. Rosenberger suggests the following classification of toxic glycosurias:

I. Kidney poisons: Phlorhizin, uranium salts, chromium salts, cantharides.
II. Asphyxial agents: Curare, methyldelphinin, acetone, hydrocyanic acid, carbon monoxid.
III. Nerve poisons: Salts, diuretics, hypnotics and narcotics (chloral, chloroform, ether, morphin, etc.). Convulsive agents.
IV. Liver poisons: Phosphorus, alcohol.
V. Unknown mode of action: Atropin, amyl nitrite, acids, etc.

Some of these agents have been found to produce glycosuria in man, but for the majority this action has been observed only in animals. The chief interest in these glycosurias lies in the demonstration of the exact mechanism of their action, or in showing that they are apt to occur in man.

Diabetes mellitus—Pancreatic Diabetes

The glycosurias thus far considered have been, for the most part, of short duration, and have been characterized either by an abnormal permeability of the kidney or by a temporary increase in the blood sugar. This increase came either from the alimentary tract or from a discharge of stored glycogen. The mild or transient character of these glycosurias leads to few serious changes in other functions of the body. Only after repeated phlorhizin injections is the glycosuria of a serious character and associated with a diminished combustion of sugar. This is apparently due to a lowered concentration of sugar in the blood and tissues.

In the more severe types of experimental pancreatic diabetes and of human diabetes, on the other hand, the glycosuria is marked and continuous; while other disturbances in the carbohydrate and fat metabolism may be present, and various nutritional disturbances in the tissues may occur. It seems probable that the body has lost to a greater or lesser extent the power to burn glucose, even when the latter is present in the blood in excessive concentration. If this be so, it represents a fundamental distinction from all other forms of glycosuria. At the present time, however, the conception of diabetes as a condition in which the ability to burn sugar is impaired has not received universal acceptance, and it seems desirable, therefore, to define human diabetes as a syndrome rather than as a specific disturbance in sugar combustion. The disease is characterized: (1) by the presence of glucose in the urine under ordinary conditions of diet; (2) by its chronic character; and (3) by the fact that the glycosuria is due to an increased concentration of glucose in the blood, a hyperglycemia.

Experimental Pancreatic Diabetes

In 1889, von Mering and Minkowski demonstrated that a total excision of the pancreas in dogs leads to a severe and fatal form of glycosuria, comparable in many ways with the human disease. Glycosuria usually develops in from two to seven hours after the operation and continues up to the death of the animal. This usually occurs in one to three weeks. The blood sugar rises from the normal for dogs of 0.08 to 0.22 per cent to an average of 0.50 per cent. When a portion, but not the whole, of the pancreas is excised, various lesser grades of disturbance in the carbohydrate metabolism may be produced. According to Allen's experience, when all but 1/10 of the gland is removed, a severe type of diabetes invariably results and sugar continues to be excreted in the urine even when the dog has been placed on a strictly meat diet. When 1/9 of the gland is left in place, severe diabetes usually results, and when 1/8 is left, severe diabetes sometimes results. In the latter case, however, there is usually either a temporary severe diabetes, or a permanent mild diabetes in which glycosuria is absent on a meat diet but present when starches are fed. A residue of 1/6 of the gland usually gives a transient mild diabetes. If 1/4 of the gland is left, no spontaneous glycosuria results but even here a diminished tolerance to subcutaneous injections of glucose can be demonstrated. Allen's experience thus indicates that a very definite relation exists between the severity of the glycosuria and the amount of pancreatic tissue left in the body.

In some experimental excisions of portions of the pancreas, the diabetes is at first mild or absent but becomes more severe as time goes on, owing to an atrophy of the residue of pancreatic tissue. This late, or Landmeyer, type of experimental diabetes is particularly apt to occur

when the blood supply to or the ducts from the glandular fragment are interfered with.

Pancreatic Influence a Chemical One.—The glycosuria resulting from pancreatectomy is not due to injury or irritation of the local nerves, but is due to a lack of some effect which the pancreas normally exerts upon the chemical processes in the body. Minkowski and others have shown that when a portion of the pancreas is transplanted beneath the skin and the remainder of the pancreas removed, no diabetes results even though the pedicle to the graft be subsequently cut. When this graft is removed the usual pancreatic diabetes follows. Pratt describes a successful transplantation of a pancreas graft in the spleen with absence of glycosuria over a period of 187 days. Evidence in favor of the chemical control exerted upon carbohydrate metabolism by the pancreas is also furnished by the results of parabiosis experiments. For example, Froschbach united pairs of young dogs in parabiosis and after firm union was established the pancreas of one was excised. Typical severe diabetes did not develop in this animal until after it had been severed from its companion. Somewhat similarly, Carlson and Drennan found that in the latter stages of pregnancy, diabetes did not follow excision of the pancreas from the mother dog but did appear shortly after removal of the puppies from the uterus. Finally, according to Carlson and Ginsberg, the injection of normal blood into an animal suffering from pancreatic diabetes causes a temporary reduction in the output of urinary sugar as well as a reduction in the hyperglycemia.

In spite of positive evidence indicating that the pancreas normally exerts a chemical influence upon carbohydrate metabolism, efforts to influence diabetic glycosuria by the use of pancreatic extracts have in general met with failure. Whether given by mouth, subcutaneously, or intravenously, these have in most instances tended to increase rather than to diminish the glycosuria.

The Pancreas in Human Diabetes

Earlier writers, notably Borchardt, Lancereaux, Windle and Frerichs, noted the occurrence of pancreatic disease in certain patients dying of diabetes. General interest in the relationship, however, was first awakened by the observation of Mering and Minkowski, that the operative removal of the gland from dogs was followed by fatal diabetes. Subsequently, numerous human cases with lesion in the pancreas were reported. At the same time it was noted that quite extensive disease of the pancreas may occur without diabetes, and that in a considerable proportion of diabetic patients no definite pancreatic lesions can be found. The problem assumed a new aspect in 1900, when Opie, as also Ssobolew, showed that in certain cases of human diabetes the pathological changes in the

pancreas were practically limited to the islands of Langerhans. These structures with special staining properties and rich blood supply are located toward the centers of the pancreatic lobules. In the embryo they develop by proliferation and differentiation of the pancreatic tubules, but in later life they are more or less distinct from the tubules proper. Whether, under pathological conditions, transitions from the one to the other can occur has not been definitely established.

Three Theories as to Character of Lesions.—Pathological studies of the pancreas in diabetic patients have led to three more or less divergent views as to the character of the lesions present in this disease. The earlier view of Hansemann that there is a *specific atrophy* of the glandular parenchyma combined with an inflammatory process in the gland is held by few pathologists at the present day. The *insular theory* which locates the distinctive lesion of diabetes in the islands of Langerhans is the dominant view at the present time, and is supported by those who have studied the largest number of cases; i. e., by Weichselbaum, who has investigated 185 cases of diabetes, Cecil 90 cases, and Heiberg 30 cases. The changes in the islands may be of a qualitative or of a quantitative character. Qualitative changes consist in hydropic degeneration, sclerosis, atrophy, and hyalin changes. Quantitative changes consist in a reduction of the number of the islands. According to the third and most recent theory, *all the epithelial tissues of the pancreas*, secreting tubules as well as islands, are implicated in the changes which lead to diabetes. Transitions between the two are assumed to occur, at least under pathological conditions.

Experimental Study of Insular Theory.—Attempts to solve the relationship of the different portions of the pancreas to diabetes by experimental methods have not been conclusive. Thus MacCallum caused an atrophy of the gland by obstructing the pancreatic duct and later excised the small remnant of atrophic tissue. Diabetes followed the second operation and in the tissue excised groups of cells were found which were interpreted as being residues of the islands of Langerhans. Milne and Peters, as well as others, however, believe that the great majority of the structures which persist after ligature are really remnants of the atrophied tubules, so that the interpretation of this experiment is uncertain. Homans has excised a large part of the cat's pancreas, leaving only a small fragment about the main duct. Most of his animals developed no diabetes and the island cells appeared to be overactive. In the few that developed diabetes the island cells appeared to be degenerated.

Diabetes Without Demonstrable Pancreatic Disease.—In any case the assumption of a specific involvement of the pancreas in all cases of diabetes meets with two objections. In the first place, extensive disease of this organ may be unassociated with diabetes and, in the second, diabetes may exist without demonstrable disease of the pancreas. In answer to

the first, it may be said that it is known that a relatively small portion (about one-sixth to one-eighth) of the gland is sufficient to protect dogs from developing glycosuria and that, furthermore, if one adopts the insular theory, extensive disease of the pancreas may occur with relatively little destruction of the islands. In answer to the second, it may be said that the number of severe cases of diabetes without pancreatic changes of any kind have become relatively few in the statistics of those who have sought for changes in recent years. Yet the undoubted occurrence of diabetes without demonstrable pancreatic disease necessitates further hypotheses. Either the carbohydrate function of the pancreas may be markedly diminished without demonstrable anatomical changes, or, in some cases at least, the essential lesion is localized elsewhere in the body.

Other Factors.—At the present time the only other parts of the body implicated in the causation of diabetes are the central nervous system or the hypophysis. That glycosuria is common in acromegaly has already been mentioned, and Gigon has collected a large number of reports showing lesions in the central nervous system of diabetic patients. Many of these were doubtless secondary or incidental to the disease, but some, and especially the severe traumata, may have been primary. Allen, also, from a few experimental observations on dogs, concludes that nervous factors may play an important part in inducing diabetes in dogs already predisposed to the disease by a partial pancreatectomy.

Hyperglycemia in Diabetes

Hyperglycemia, an increased concentration of blood sugar, is now recognized as a fundamental disturbance in diabetes. In place of the normal concentration of 0.07 to 0.11 per cent, the concentration in diabetes ranges from 0.12 to 0.40 per cent or over. High concentrations of blood sugar are usually associated with marked glycosuria, but no exact parallelism exists between the two. The blood concentration which must be reached before the kidney begins to excrete sugar into the urine, and the quantity excreted after this threshold has been passed, are both subject to rather wide variations not only in different diabetic patients, but also in the same patient at different times. In diabetic coma especially, the discrepancy is apt to be very marked with high glycemia and relatively low glycosuria. For example, Liefmann and Stern have reported a remarkable case of coma with 1.01 per cent of sugar in the blood and with but traces in the urine, and similar though less marked discrepancies have been reported by others. The kidneys, which commonly show other evidences of damage in coma, seem to acquire a considerable impermeability to the excess of blood sugar.

Renal Threshold in Chronic Diabetes.—In the normal individual the threshold above which the kidneys usually begin to excrete sugar is commonly placed at 0.12 to 0.18 per cent of glycemia, but this level is not

a fixed quantity. In diabetic patients the variations in this threshold are also marked. With hyperglycemias ranging from 0.12 to 0.20, the excretion of sugar may vary from considerable quantities to zero. Von Noorden believes that when the disease has been present for a long time the urine is more apt to be sugar free at higher levels of glycemia. His figures are shown in the following table:

Duration of the Disease	Blood Sugar with Absence of Glycosuria
10–15 years	0.189%
4–5 years	0.175
1–3 years	0.143
Less than one year	0.109

With the progress of the disease, therefore, there seems to be a tendency for the kidneys of diabetic patients to become more impermeable to moderate rises of the blood sugar and this occurs even though no clinical manifestations of nephritis are present. In birds (geese) this relative impermeability of the kidneys to blood sugar is normal, for in these animals excision of the pancreas is not ordinarily followed by glycosuria even though the blood sugar rises from the normal of about 0.15 per cent to 0.50 per cent.

It is obvious, therefore, that the disappearance of a diabetic glycosuria gives no assurance that the blood sugar has returned to the normal level. In some patients this does indeed occur; in others the hyperglycemia may disappear only after prolonged adherence to the strict diet.

Classification of Diabetes

It is customary to classify the severity of human and of experimental pancreatic diabetes according to the ease with which the sugar can be made to disappear from the urine as a result of dieting.

Severe Form.—In some patients the glycosuria persists after the elimination of all carbohydrates from the food. These patients are said to have a severe form of the disease. In most of these severe cases a further restriction of the protein intake eliminates the last traces of sugar from the urine. Less commonly, the glycosuria persists despite exclusion of carbohydrates and a marked restriction of the proteins. Complete starvation, however, nearly always causes the urine to become sugar free. Estimates of differences in the more severe cases have also been made by determining the relation which exists between the amount of protein metabolism and the amount of sugar elimination (D: N ratio, page 281).

Mild and Moderately Severe Forms.—When the sugar disappears from the urine of a diabetic on a diet free of carbohydrates, bread or some other carbohydrate food is given in ascending quantities and the point is noted at which glycosuria reappears. If the patient's urine is

free of sugar on a carbohydrate free diet and if glycosuria appears when less than 100 grams of white bread are added to the diet, the condition is classified as one of moderate severity. If the patient will tolerate 100 grams of white bread or more without the appearance of sugar in the urine, the patient is said to have a mild form of the disease. In very mild cases 200 grams of bread or over may be taken without having sugar appear in the urine. Should, however, glycosuria occur when the individual takes large quantities of starchy food with his meals, the patient cannot be regarded as normal, for the normal individual apparently tolerates unlimited quantities of starch when taken with other foods.

Incipient Form.—When glycosuria occurs only after the ingestion of large quantities of sugar, this may or may not indicate an incipient form of true diabetes. A negative test after feeding 100 grams of glucose is presumptive evidence of the absence of true diabetes, but as we have seen the test does not always hold [illegible] (page [illegible]).

Variations in Carbohydrate Tolerance.—While the above tests afford a convenient method for classifying diabetic patients according to their tolerance for carbohydrate food, it must not be assumed that this tolerance is an invariable quantity in an individual patient. Of the factors that influence tolerance, the most important is the degree to which the functions [illegible] are weakened. The neglect of dietetic regulation resulting in a constant excretion of glucose in the urine, tends to decrease the tolerance. On the other hand, the adherence to a strict dietetic regime tends to improve the tolerance. Allen has recently recommended [illegible] periods of starvation in the treatment of diabetes. [illegible] usually become sugar free after several days of [illegible] starvation. By adding in succession green vegetables, [illegible] requirements, and later fats, it is frequently possible to keep the urine free of sugar, even when moderate amounts of [illegible] are being taken. In this manner patients [illegible] according to the above standards [illegible] by reason of the fact that [illegible] take moderate or considerable (over 60 grams) quantities of starch.

The Derivation of Sugar in Diabetes

[illegible] diabetic patients is [illegible] is derived [illegible] Different foods [illegible] and [illegible] is increased by giving a [illegible] is itself the source of [illegible] mind that a substance

may stimulate the production or liberation of sugar in the body without being its immediate source. Adrenalin, for example, exerts such an action, and in recent years a comprehensive application of this view to certain foodstuffs has been proposed by von Noorden and his school. We shall see later (page 288) that this theory as applied to foodstuffs has not met with great favor and for the present we may assume, that when a food produces or increases glycosuria it does so by being itself the source of extra glucose in the body.

Carbohydrates

As might be expected, foods which yield glucose during the process of digestion tend, in general, to increase a preëxisting glycosuria and to produce glycosuria in normal, and especially in mildly diabetic individuals. The degree of glycosuria which follows the feeding of various carbohydrates does not run exactly parallel to the amounts of glucose which may be derived from them. Sugars in general, and especially glucose and maltose, which latter yields two molecules of glucose, are particularly apt to produce increases in glycosuria.

Oatmeal Treatment.—Among starches, oatmeal seems to be relatively well borne by certain diabetics, and the oatmeal treatment has been extensively used by von Noorden and others. The relatively good tolerance of oatmeal by certain diabetic patients is particularly evident when other starches are withheld, and when the proteins of the diet and especially the meats are restricted.

Cause of Differences in Carbohydrates.—The cause for the varying degrees of glycosuria which follow the administration of equivalent amounts of different carbohydrates is not well understood. Beyond doubt, they depend in part upon the rate of absorption from the intestines. Anything that will delay this absorption permits the body to take care of a greater amount of glucose, whereas a rapid absorption quickly raises the level of glucose in the blood and tends to cause or to increase a preexisting glycosuria. Among factors which influence the rate of absorption are: (1) the speed with which the stomach empties its contents into the intestines; (2) the stimulus to pancreatic secretion; and (3) the digestibility of the starches taken. Jacobson has shown that the simple addition of a large quantity of butter to bread will delay the time and diminish the amount of the subsequent hyperglycemia, owing to the delay in digestion caused by the addition of fat. Possibly the favorable effect of opium upon the glycosuria of diabetic patients is due in part to the action of this drug in delaying the exit of food from the stomach. Cohnheim and Klee have shown that oatmeal calls forth relatively little pancreatic secretion. Not only is its digestion thereby delayed, but the pancreas by reason of the smaller external secretion furnished may be

the better able to perform its internal function of carbohydrate assimilation. Whether certain starchy foods, and particularly oatmeal, contain additional substances which assist in the assimilation of glucose, or whether some peculiar configuration of certain starch molecules plays a part in their value as diabetic foods, are at the present time open questions.

Proteins

That sugar may be formed in the body from sources other than the carbohydrates taken in the food has been abundantly proven. Studies conducted upon patients with diabetes, and upon animals that have been depancreatized or phlorhizinized, have shown repeatedly that the amount of sugar excreted in the urine during prolonged carbohydrate starvation may be far in excess of the amount that could possibly have been derived from carbohydrates stored in the body at the beginning of the experiment. Thus Lüthje describes an experiment in which, after pancreatectomy, a dog placed on a diet free of carbohydrates excreted a total of 1,175 grams of sugar over a period of about four weeks. The preformed glycogen was calculated to be not more than 232 grams, which amount corresponds to 257 grams of sugar. The sugar derived from other sources, therefore, was not less than 919 grams.

Source of This Sugar.—As possible sources for this sugar, proteins and fats must be considered. The view that sugar may be derived from protein is made probable by various types of experiment. Pflüger long maintained that the derivation of sugar from proteins had not been proved; but in 1910 he with Junkersdorf showed that the liver glycogen is markedly increased after feeding veal, a meat which contains a very small per cent of glycogen. Their experiments are summarized in the following table:

	Average Per Cent of Glycogen	
	Liver	Muscles
Dogs killed on the 11th day of fasting	0.59	0.21
Dogs (10) fasted 10 days, given phlorhizin on the 8th, 9th and 10th days, and killed 7 hours after	0.05	0.198
Dogs (38) fasted and phlorhizinized as before, but killed 24 hours after last dose	1.1	0.37
Dogs (27) fasted and phlorhizinized as before. Twenty-four hours later given 400 grams veal and killed 8 hours later	2.25 to 2.44	0.22 to 0.31
Dogs treated as before, but given still larger amounts of veal	6.46	1.0

In similar experiments they found that the ingestion of fats did not increase the glycogen content of the liver.

The D:N Ratio

Experiments on patients with severe diabetes, on depancreatized animals and upon phlorhizinized animals, have all shown that following the ingestion of meats there is a marked increase in the excretion of sugar in the urine. Indeed the relationship between the urinary dextrose and nitrogen, the so-called D: N ratio, is frequently so constant as to suggest the possibility that by this method one might measure the amount of sugar which is derived from proteins in the animal body. Were all of the carbon present in the protein molecule, after subtraction of urea (or ammonia), converted into dextrose, relatively large amounts of glucose could be formed from proteins; and if all of this sugar appeared in the urine, the D:N ratio would approach 8. As a matter of fact, lower ratios have in general been found. In his studies on depancreatized dogs, Minkowski showed that when these animals were fasting, or when they were placed on an exclusive meat diet, the D: N ratio was about 2.8.

In Phlorhizinized Animals.—Similarly Lusk and his coworkers found that when animals are given sufficient doses of phlorhizin at frequent and regular intervals the D: N ratio becomes fairly constant after the first day of the experiment. For rabbits, cats and goats this constant ratio was about 2.8, but for dogs it was approximately 3.6. The following table illustrates how constant the ratio may remain when gelatin is fed to a phlorhizinized dog:

	Urinary			
	D	N	D:N	N Loss
Hunger	21.2	5.76	3.67	5.76
60 g. gelatin	35.8	9.70	3.69	1.18
Hunger	17.3	4.80	3.59	4.82

Similar results have been obtained with other proteins, such as meat and casein. In all such experiments fluctuations in the D: N ratio are apt to occur. These may be due to a formation of extra sugar from glycogen still present in the body or they may be due to some retention of carbohydrates or of nitrogenous products that are derived from the protein metabolism. These discrepancies tend to disappear during longer periods of observation under constant conditions. The relatively high D: N ratio of phlorhizinized dogs, i. e., 3.6, sometimes falls to the lower level of 2.8. The exact cause of this change is not known, but it is interesting to note that Jackson as well as Loewi has produced such depressions by administering camphor.

It is remarkable that two distinct levels for the D: N ratio should exist in different classes of animals or even under special circumstances in dogs alone. Since dextrose is probably synthesized from certain of the amino acids derived from the disintegration of proteins in the body, Lusk has suggested that the different levels of the D: N ratio may depend upon the ability of the body to convert certain of these amino acids into dextrose.

Ratio in Human Diabetes.—In very severe types of human diabetes the D: N ratio has generally shown considerable variations, not only in different patients but in the same patient from day to day. The variations between different patients doubtlessly depend in part upon variations in the severity of the disease, and the determination of the D : N ratio during a prolonged carbohydrate free diet has been recommended as a measure of the severity in serious cases. The fluctuations from day to day probably depend in large measure upon varying retentions of sugar or of nitrogenous products in the body. Such retentions seem more prone to occur in the human disease than in experimental studies, due perhaps to the more complex nature of the disease. In the majority of human cases the D:N ratios have been found to be less than 3.85, and Mendel and Lusk regarded this ratio as a "total" diabetes. More recent studies by Falta and his coworkers, by Grafe and Wolf, and by others have shown that D: N ratios of 5 and over may persist for some time in diabetic patients. The explanation for these unusually high ratios is not certain. It is difficult and usually inadvisable to subject diabetic patients to such rigid experimental conditions as can be carried out in animals; and it is always difficult to eliminate such possibilities as a conversion of preformed glycogen into sugar, retention of substances in the body and the surreptitious ingestion of carbohydrates by the patient. Could these sources of error be eliminated, two explanations for the very high D: N ratios occasionally observed in diabetic patients seem possible. Either an unusual quantity of sugar has been formed from proteins or a conversion of fats into glucose has taken place.

Formation of Sugars from Proteins.—By what chemical transformations are sugars formed from proteins in the animal body? The view that the urinary sugar is derived solely from some preformed carbohydrate radicle such as can be split off from certain proteins by acids, has been definitely abandoned, because the amount of sugar eliminated bears no constant relation to such preformed carbohydrates. Casein which yields no sugar by such treatment, gives rise to large increases of sugar when fed to depancreatized or phlorhizinized animals. It is now known that the protein molecule is made up of a large number of simpler compounds, chiefly amino acids. During the process of protein disintegration in the body, these simpler compounds are set free and it is from these building stones that the animal body forms glucose by a

process of deaminization and synthesis. Ringer and Lusk have shown that certain of these building stones, viz., glycocoll, alanin, aspartic acid and glutamic acid, are converted more or less completely into sugar in phlorhizinized dogs.

Fats

Fats are composed of glycerin united with fatty acids, and the separate effect of these components upon sugar production in the body must be considered. Lüthje showed that the feeding of glycerin to depancreatized dogs was followed by an increase in the excretion of sugar, and Cremer found the same to be true when it was fed to phlorhizinized animals. Yet glycerin forms but an insignificant proportion of the weight of fats (less than 10 per cent), so that the derivation of sugar from this portion of the fat molecule would be without great practical significance.

Glycosuria Not Increased by Fats or Fatty Acids.—In contrast to glycerin, to carbohydrates and to proteins, the feeding of fats or fatty acids does not increase the glycosuria either in diabetic patients or in depancreatized or phlorhizinized animals. Indeed the glycosuria may diminish owing to a reduction in protein metabolism. It is indeed possible that fats may still give rise to sugar, for the ingestion of fats, unlike that of proteins, causes no very marked increase in fat metabolism; but, up to the present, no conclusive evidence that sugar may be derived from fatty acids has been furnished. The very high D : N ratios observed occasionally in human diabetes may, as we have just seen, be explained upon other grounds.

The Energy Requirements in Diabetes

Inasmuch as a regulation of the diet is essential in the treatment of diabetes, it is important to know how much energy diabetic patients require and in what form this energy can best be furnished. The metabolism of depancreatized dogs, studied by Falta and his coworkers, by Ringer and by others, shows a number of departures from the normal. There is an increase in the total metabolism, in the protein decomposition and in the excretion of salts. But in human diabetes it has been uncertain whether the total metabolism was normal, increased, or diminished. The recent work of Benedict and Joslin has demonstrated that in the severer forms of the disease there is a slight but distinct increase in the energy requirements. Nineteen patients with severe types of diabetes were studied, and their rates of metabolism were compared with the rates of normal individuals of corresponding weight and height. The patients with severe diabetes showed quite regularly a somewhat higher rate of metabolism than the normal controls. The average values of these determinations are tabulated on page 284.

	CO_2 per Kilo per Minute	O per Kilo per Minute	Heat Eliminated per Kilo in 24 Hours	
			Sitting	Lying
	c.c.	c.c.	cal.	cal.
Normal subjects	3.13	3.72	29.0	24.2
Severe diabetes	3.31	4.49	33.6	27.6
Percentage increase in severe diabetes	6	20	15.7	13.9

Increased Basal Metabolism.—Since the consumption of oxygen is a better indicator of the heat produced in metabolism than is the elimination of carbon dioxid, it seems proven that in severe diabetes the basal metabolism is from 14 to 20 per cent greater than it is in normal individuals under comparable circumstances. In the milder cases of diabetes studied by these authors, some increase in the rate of metabolism appeared to be present, but this was less certain and less marked than in the more severe forms of the disease.

Benedict and Joslin have attributed the increased rate of metabolism in severe diabetes to the acidosis present. Even normal individuals show a definite rise in metabolism when an acidosis is produced by restricting the carbohydrate intake.

The Energy Supply in Diabetes

In diabetes a part of the energy supplied by the food is lost as dextrose in the urine. In the milder forms of the disease these losses are not in themselves of serious moment. A proper restriction of the carbohydrate intake eliminates the sugar losses in the urine, and even though no dietary restrictions are practiced the urinary losses may often be covered by a more abundant diet. Thus many patients with the milder types of diabetes show no loss of weight or strength over long periods of time, and gains in weight are not infrequent. The increased appetite compensates or overcompensates for the energy losses in the urine. In such patients the dangers of the disease consist not so much in loss of food material by way of the urine as in a liability to the various complications, such as infections, gangrene, nervous and ocular changes. A disregard of dietary regulations also favors the progress of the disease, in accordance with the general principle that when a weakened function is overburdened it tends to become still further weakened.

Maintenance of Body Weight.—In severe types of diabetes, on the other hand, where the power to utilize carbohydrates is more seriously impaired, the maintenance of body weight becomes a far more difficult

problem. Not only do such patients require from fourteen to twenty per cent more energy than do corresponding normal individuals, but the losses of energy through the urine are more difficult to regulate. If large quantities of carbohydrates are given in the diet they cause a large sugar elimination which may equal the amount taken. As a source of bodily energy, therefore, they have a very restricted value, and the amount that can be taken advantageously is always limited. Furthermore, in severe cases proteins also increase the sugar output in the urine. In extreme cases where the ratio between urinary sugar and protein intake is high, as shown by a D:N ratio of 2.8 to 3.6, from 40 to 60 per cent of the energy contained in the proteins burned is lost as sugar in the urine. Finally, in conditions of marked acidosis, the loss of energy in the form of beta-oxybutyric acid and related bodies may be considerable.

It is, therefore, evident that a maintenance of the energy requirements in the most severe types of diabetes becomes a matter of great difficulty. The greater part of the carbohydrates taken is lost in the urine, as is also a considerable proportion of the energy contained in the proteins or even the fats. It is in such cases that much dietetic and therapeutical skill is required in order to supply the patient with sufficient nourishment. Obviously fat must play a predominating part in the diet and, in addition, the tolerance of the patient to various proteins and starches must be carefully studied. It is particularly in this group of patients that differences in the utilization of various proteins and starchy foods assume great practical significance. While there seem to be individual differences among diabetic patients as regards sensitiveness to different proteins and starches, it is a general rule that meat is less well borne than are the proteins of vegetables or eggs. Also a restriction to one type of starchy food, and especially oatmeal, is frequently attended with better results than where mixtures of starches or combinations with meats are given.

The Glycogen in Diabetes

After complete extirpation of the pancreas, the amount of glycogen in the liver rapidly diminishes. In a few days only traces remain but these persist and do not entirely disappear. The muscle glycogen is also reduced in amount but less markedly so than the liver glycogen. On the other hand, there is an increase in the glycogen content of the leukocytes and of the kidneys, due apparently to the increased concentration of glucose in the blood. Minkowski has shown that when glucose is fed it does not increase the glycogen in the liver of depancreatized dogs, whereas the feeding of levulose produces such an increase. Since the glycogen in the latter case apparently differs in no way from that found normally, it would seem that the pancreas exerts a specific influence upon the formation of glycogen from dextrose and that this pancreatic influ-

ence is not equally essential in the case of levulose. In depancreatized animals, therefore, the ability to store glucose as glycogen is markedly reduced. When sugar is introduced into the circulation of normal animals it rapidly disappears from the blood, whereas in depancreatized animals the glucose content of the blood is not promptly reduced after the introduction of sugar (Kleiner and Meltzer). That this inability to remove glucose from the blood favors glycosuria cannot be doubted; but it is insufficient in itself to explain the severe and persistent glycosuria which follows experimental removal of the pancreas.

Glycogen in Human Diabetes.—It is difficult to ascertain the exact amount of glycogen stored in the liver and muscles of diabetic patients, partly because glycogen is rapidly converted into glucose after death, and partly because the period of undernutrition which usually precedes death would in itself tend to reduce the glycogen. It seems probable, however, that in diabetic patients as in the depancreatized dog there is a reduction of the amount of glycogen stored in the liver and muscles. That the ability to store glycogen is not entirely lost is attested by the fact that, even in severe diabetes, the administration of carbohydrates may increase the glycosuria for several days thereafter.

The Respiratory Quotient in Diabetes

We have already seen that, in the combustion of food materials, the relation between the volume of carbon dioxid given off and the volume of oxygen consumed varies according to the type of food burned. This ratio, which is known as the respiratory quotient, is for carbohydrates 1.0, for fats about 0.7 and for proteins about 0.8. With certain reservations, discussed elsewhere (page 208), an examination of the gaseous interchange by way of the lungs furnishes data concerning the nature of the body metabolism. A high respiratory quotient indicates a predominance of carbohydrate metabolism, while a ratio lying between 0.7 and 0.8 indicates the predominance of a fat-protein combustion. In complete starvation, for example, after the main portion of the glycogen reservoirs of the body has been exhausted, the ratio falls to 0.74 or less, owing to the combustion of the fats and proteins of the body.

Reduction in Diabetes.—In diabetes the respiratory quotient tends to be reduced, and in Benedict and Joslin's series of nineteen cases of severe diabetes the average respiratory quotient, without taking food on the day of the experiment, was 0.74, while their normal controls showed an average of 0.81 under similar experimental conditions. The higher ratio in the latter individuals was evidently due to a consumption of glycogen previously stored in the body.

In normal men and animals the consumption of a large carbohydrate meal causes the respiratory ratio to rise markedly, so that it approaches

or equals 1.0. In severe cases of diabetes, on the other hand, no such marked rise occurs after the feeding of carbohydrates, and in the most severe cases the respiratory quotient is almost unaffected by the ingestion of carbohydrates.

In severe cases of diabetes mellitus, therefore, the respiratory quotient is such as one finds when an individual is living on a protein-fat diet. Furthermore, this quotient is raised little, if at all, by the feeding of carbohydrates.

Effects of Exercise

After incomplete extirpation of the pancreas, muscular exercise tends to diminish the sugar excretion in the urine, apparently because the muscles consume an increased amount of sugar from the body fluids. After complete extirpation, on the other hand, Seo found that exercise did not affect the total amount of sugar excreted during the course of the twenty-four hours. Similar observations have been made upon diabetic patients. In the milder types of the disease exercise tends to diminish the glycosuria. In the severer types, on the other hand, the effect is less marked, and von Noorden describes six severe cases in which the glycosuria was somewhat increased by exercise. Respiratory experiments on his patients by Salomon showed that during exercise the respiratory quotient did not show the rise which occurs in normal individuals, thus indicating that the energy consumed during the exercise did not come from a combustion of carbohydrates.

Theories of Diabetes

We have seen that the immediate cause of the glycosuria in diabetes mellitus is an increased concentration of sugar in the blood. This diabetic hyperglycemia occupies a central position in any discussion concerning the nature of diabetes mellitus. We have seen, furthermore, that in experimental pancreatic diabetes, and probably in human diabetes as well, the glycogen storage in the liver and muscles is subnormal, although the ability to store carbohydrates is not entirely lost. Since transitory glycosurias of various types may occur from a discharge of the glycogen reservoirs, the question arises whether a deficient storage capacity for glycogen could account for the glycosuria of diabetes. It is certain that a deficient storage of glycogen plays a part in the hyperglycemia that follows the ingestion of food. This defect in itself, however, could hardly produce more than a transitory or intermittent glycosuria. In more severe types of diabetes, sugar is excreted in such large amounts and for such long periods of time, that it could not possibly have come from a defective carbohydrate storage in the body.

Diminished Combustion of Glucose.—The more continuous forms of diabetic glycosuria can be explained on either of two hypotheses: first,

a diminished consumption of sugar; and, second, an increased production of sugar in the body. The theory of a primary reduction in the capacity of the diabetic body to burn sugar is, at the present time, the more generally accepted view, and it affords a simple explanation for most of the well-established observations on the disease. The low respiratory quotient observed in severe cases, and the failure of this quotient to rise either during muscular exercise or after the ingestion of carbohydrate food, accord well with this hypothesis. The immediate increase in glycosuria after taking carbohydrates, and the fairly constant D:N ratio observed after pancreatectomy, are readily explained on the assumption of a reduced combustion of sugar. Finally, as we shall see, the acidosis so common in severe diabetes is best explained on the assumption of a diminished sugar combustion. The assumption of a primary inability to burn sugar on the part of the diabetic body does not exclude the possibility that an increased production of sugar may occur as a secondary phenomenon. The tissue cells, unable to burn sugar, may excite an overproduction.

Increased Production of Glucose.—The hypothesis of a primary overproduction of sugar in the body has been recently revived and defended by von Noorden and others. According to this hypothesis, there is normally a constant formation of sugar chiefly in the liver, one of its important sources being fat. In depancreatized animals and in human diabetes it is assumed that this production is excessive, and that it is stimulated by the ingestion of carbohydrates and proteins, as well as by nervous and glandular influences. The body burns sugar normally; but, owing to the overproduction, hyperglycemia and glycosuria are produced. In support of this hypothesis, special importance has been attached to the experiments of Porges and Salomon, who found that when the circulation was cut off from the abdomen of depancreatized dogs the respiratory quotient rose to 1.0. This was taken to indicate that the tissues of depancreatized animals possessed a normal ability to burn carbohydrates. Manifestly, however, much uncertainty is attached to conclusions drawn from studies on animals subjected to this serious operation. Rolly, who has repeated these experiments, was unable to obtain constant results, and he has suggested other explanations for the high respiratory quotient. It has also been claimed that epinephrin stimulates the liver to an overproduction of sugar, and that the glycosuria of diabetes may be compared to that produced by epinephrin. Yet Ringer found no increased production of sugar when epinephrin was given to glycogen free, phlorhizinized animals, so that it is doubtful if epinephrin has this action. Finally, the very high D:N ratio occasionally encountered in human diabetes is said to indicate an excessive formation of sugar from fat. Here again, however, other explanations are possible (page 282). Altogether, the arguments adduced in favor of the hypothesis that the primary disturbance

in diabetes is an overproduction of sugar rest on an insecure basis, and, for the present at least, it seems more probable that the essential disturbance consists in an inability to burn sugar. An insufficiency of the glycogen reservoirs and a secondary increase in sugar formation may play secondary rôles in the pathogenesis of the disease.

Symptoms and Complications of Diabetes

Emaciation and Polyphagia

Satisfactory explanations can be given for certain complications of diabetes mellitus only. The frequent emaciation and excessive appetite are due to an insufficient nutrition of the tissues. It has been pointed out that in severe forms of the disease the energy requirements of the body may be increased by from fourteen to twenty per cent, and that it may be difficult to cover these requirements, because a considerable proportion of the energy contained in the food is lost to the body in the form of urinary sugar. The tissues starve, in spite of the fact that they are surrounded by a fluid abnormally rich in glucose. In the milder types of diabetes the sugar losses that result from improper dieting may be covered, or more than covered, by eating excessive quantities of food. It therefore happens not infrequently that patients with the milder forms of the disease maintain a normal weight, or even gain in weight, owing to a good appetite. In such cases a restriction in the carbohydrate food, sufficient to eliminate sugar from the urine, often makes it possible for the patient to maintain his normal weight without the ingestion of unusual quantities of food. It has been shown by Luckhardt that the excessive hunger of depancreatized dogs is due to increased hunger contractions of the stomach.

Polyuria and Thirst

Polyuria and thirst, which are among the commoner symptoms of diabetes mellitus, are intimately associated with each other. The polyuria is primary, and the thirst is caused by the losses of water through the kidneys. Apparently these losses affect the water contents of the tissues rather than the blood, for in diabetes the percentage of water in the blood is usually about normal. Von Noorden gives the following table to show the approximate relation which he has observed between the quantity of urine and the degree of glycosuria:

Amount of Urine	Specific Gravity	Percentage of Sugar
1,500– 2,500	1.025–1.030	2–3
2,500– 4,000	1.030–1.036	3–5
4,000– 6,000	1.032–1.040	4–7
6,000–12,000	1.036–1.046	6–9

It is obvious that the polyuria varies with the amount of sugar excreted through the kidneys. Considerable variations exist in each of the above classes, and it is not uncommon to find three per cent, or more, of sugar without a definite increase in the urine. When the glycosuria is caused to disappear by a suitable diet, the polyuria and thirst usually disappear at the same time.

Diuretic Action of Sugar in Diabetes.—In diabetes as in normal individuals an excess of sugar in the blood acts as a diuretic, causing an increase in the elimination of water. Its action is analogous to the effect of certain salts which are excreted through the kidneys. Allen believes that this diuretic action of sugar is a specific characteristic of diabetes. According to this author, sugar acts as a diuretic in normal animals only when it is introduced directly into the blood stream. When it is absorbed from the intestines, the subcutaneous tissues, or the peritoneal cavity, it tends to diminish rather than to increase diuresis. In depancreatized animals, Allen found that sugar acts as a diuretic, however it be introduced, and he concludes that in these latter the sugar of the blood exists in the free state, while under normal conditions it is present in a colloidal combination that is formed during its absorption.

Diminished Resistance to Infection

Diabetic patients are peculiarly liable to various infections, particularly boils, tuberculosis, and postoperative infections. This increased susceptibility has frequently been attributed to the increased percentage of sugar in the body fluids which are said to furnish a better culture medium for invading microörganisms. The validity of this explanation may, however, be questioned. The addition of such small amounts of sugar to the blood as occur naturally in diabetes mellitus does not, as a rule, improve its cultural properties. The poor resistance to infection seems to depend rather upon a diminution in some of the protective properties of the blood. Da Costa and Beardsley found that in diabetes mellitus the opsonic index was diminished, and that it was particularly low in the more severe cases studied. This reduction in protective properties does not seem to be a direct result of an increased amount of blood sugar, for Handmann found that the addition of sugar to blood in vitro did not diminish its bactericidal or opsonic properties, and Sweet found that while the bactericidal properties of blood are not changed by the hyperglycemia induced by epinephrin injections, they are definitely diminished after excision of the pancreas. It seems probable, therefore, that the lack of resistance to infection so frequently exhibited by diabetic patients depends not directly upon the hyperglycemia, but upon some effect exerted by the disease upon the formation of protective substances, bactericidal or opsonic, in the body.

Nutritional Changes

Diabetes is frequently complicated by conditions which seem to depend upon nutritional disturbances or upon some obscure toxic effect. That arteriosclerosis is relatively frequent in long-continued cases of mild diabetes has been abundantly proven by clinical experience, and it is well known that vascular changes are mainly responsible for diabetic gangrene of the feet. The experimental production of cataract by injections of sugar solutions into frogs was first accomplished by Weir Mitchell in 1860. It has been produced in other animals by Heubel, who also showed that such cataracts were due to osmotic changes and could be produced by other substances. Opacities of the lens produced in this manner are, however, probably not related to the cataracts which occur naturally in diabetic patients. These latter seem to depend upon some obscure changes in metabolism. The not infrequent complication of diabetes with obesity or with gout also indicates that this disease is apt to be associated with other metabolic disorders.

Lipemia.—Interesting and important changes frequently occur in the fat metabolism of diabetic patients. The insufficient burning of fats which gives rise to the acetone group of substances and to diabetic coma will be considered in the next section. In addition, there is not infrequently an increase in the fatty substances of the blood, and a visible milkiness of the blood serum, lipemia, may result. The cholesterin of the blood serum is increased, particularly in the more severe cases. Deposits of cholesterin in the skin may give rise to xanthomata.

The Acetone Bodies

Diabetic Coma

Various types of coma may complicate diabetes mellitus; but the most common, the most characteristic, as well as the most feared type is that which has been designated specifically as diabetic coma. This is a well-defined clinical entity, characterized by unusually deep respirations (the air hunger of Kussmaul), by a mortality approaching 100 per cent, and by the presence of the so-called acetone bodies in the tissues, blood, urine, and expired air. Acetone was discovered in the urine of patients suffering from diabetic coma by Petters in 1857. In 1865 C. Gerhardt described the ferric chlorid reaction of the urine, and the substance giving rise to this reaction was identified as aceto-acetic acid by Tollens in 1881. Finally, in 1883, Stadelmann demonstrated that large quantities of organic acids were present in the urines of patients suffering from diabetic coma, and, in the same year, beta-oxybutyric acid was shown to be the principal of these by E. Kulz and by Minkowski. These three sub-

stances, acetone, aceto-acetic acid, and beta-oxybutyric acid, are closely related chemically, and they frequently occur together in the animal body. They are often spoken of collectively as the acetone bodies, and when they occur in the urine the condition is often designated as ketonuria. Little doubt now exists but that they are responsible for true diabetic coma. The sources from which they are derived, the factors favoring or retarding their formation, and the exact manner in which they produce coma, have been important subjects of modern investigation.

Conditions in which the Acetone Bodies Occur

Small quantities of acetone are frequently found in the urines of normal individuals and are without pathological significance. In certain conditions, however, physiological as well as pathological, the amounts are markedly increased, and it is necessary to review these before we consider the origin and significance of the acetone bodies in diabetic coma.

Ketonuria from Carbohydrate Starvation.—The best studied type of ketonuria is that induced by carbohydrate starvation. In absolute starvation, acetone appears in the breath and urine a few days after food is withdrawn (depletion of body glycogen), and it is shortly followed by the appearance of aceto-acetic and beta-oxybutyric acids. This ketonuria of starvation may be prevented by the administration of various carbohydrates in quantities approaching 100 grams a day. Such quantities are not in themselves sufficient to maintain the body nutrition, yet they prevent the appearance of the acetone bodies in the urine. This shows that the ketonuria of starvation depends, not upon insufficient nutrition in general, but upon an insufficient supply of carbohydrate food. Conversely, if carbohydrates be excluded from the diet but the caloric requirements of the body be covered by ample amounts of proteins and fats, then the acetone bodies usually appear in the urine just as they do in complete starvation. In such a diet, a relatively large quantity of meat tends to diminish the ketonuria, apparently because proteins give rise to glucose or other bodies which have this inhibitory action. The ketonuria which follows the withdrawal of carbohydrates from the diet of a normal individual is more marked if this withdrawal be done suddenly, and if the individual has previously been on a diet rich in carbohydrates. Furthermore, if carbohydrates continue to be excluded from the diet, the acetone bodies in the urine tend to diminish as time goes on and may ultimately disappear. In many instances at least, the human body seems able to accustom itself to a properly adjusted fat-protein diet; which is indeed the normal diet of the Esquimaux as well as of carnivorous animals.

Considerable differences exist among various normal individuals in regard to the degree of ketonuria which follows the complete withdrawal of carbohydrates from the diet. In some the ketonuria is slight. In others, as Forssner and Landergren have shown, carbohydrate starvation

increases the excretion of acetone bodies to over forty grams a day (calculated as beta-oxybutyric acid) and produces distinct toxic symptoms. Such quantities are of the same magnitude as those that are excreted by many diabetic patients previous to the onset of coma. The cause of these individual variations in susceptibility to carbohydrate withdrawal is not well understood.

Pathological ketonurias, more or less marked in degree, have been observed with greater or less frequency in a great variety of conditions. Among these may be named fevers, malignant tumors, gastro-intestinal disorders, eclampsia, phosphorus poisoning, after narcosis, etc. In many of these conditions the ketonuria is caused, or at least favored, by a concomitant partial starvation. This is true, for example, after anesthesia, during many fevers, and in many gastro-intestinal disturbances, especially when there is persistent vomiting. In diabetes also the ketonuria is undoubtedly dependent in large part upon carbohydrate starvation; for even though the body fluids contain an excess of glucose, the cells seem unable to utilize it and, therefore, starve in the midst of plenty. As a rule, ketonuria is most marked in the severe cases, where the ability to burn sugar is most reduced.

The ketonuria of severe diabetes is usually increased by an abrupt change to a diet that contains no carbohydrates but does contain large quantities of fats and proteins. The danger of inducing diabetic coma by making such an abrupt change in patients already showing a considerable ketonuria is well recognized and the importance of making the change gradually is now generally recognized. On the other hand, according to Allen, complete starvation of a diabetic patient tends to reduce a preëxisting acidosis. The cause for this difference in the reaction to complete starvation from that shown by the normal individual is not well understood. It would appear, however, that when the excessive load on the carbohydrate metabolism is reduced by starvation, there is an improvement not only in the patient's ability to handle carbohydrates but also in his ability to burn the ketone bodies or their antecedents.

Ketonuria from Other Causes.—Many writers have maintained that carbohydrate starvation is the sole cause of ketonuria and that in the last analysis all cases will be shown to be due to this cause. Certain forms, however, are difficult to explain on this hypothesis. This is particularly true of the ketonuria associated with periodic vomiting. This condition, which usually occurs in children, is characterized by recurring attacks of severe vomiting. As prodromal symptoms the child often becomes nervous and irritable, he sleeps poorly, the appetite is lost and the bowels become constipated. During the attack the vomiting is frequent and persistent, the liver is often enlarged, and the urine contains all of the acetone bodies. Edsall, Hecker and others have shown that in these children the ketonuria may precede the attack of vomiting.

These patients may also eat carbohydrates well up to the onset of the attack. It would appear, therefore, that, in the periodic vomiting of infancy and childhood, there is no reason to assume that the ketonuria depends primarily upon carbohydrate starvation. Mild degrees of ketonuria are not uncommon after the administration of narcotics. Occasionally, however, a very severe and characteristic set of symptoms associated with marked ketonuria follows the administration of an anesthetic and especially of chloroform. The patient becomes jaundiced, may have convulsions, passes into coma, and frequently dies. At autopsy an extensive degeneration of the liver is found. This type of ketonuria, as well as that seen in the somewhat similar complex produced by phosphorus poisoning, is apparently not influenced by the administration of carbohydrates.

These conditions, the periodic vomiting in childhood and the severe hepatic degeneration of chloroform and of phosphorus poisoning, furnish the best examples of high degrees of ketonuria without evident dependence upon carbohydrate starvation. In them, the ketonuria is not relieved by the administration of carbohydrates. It is true that a temporary failure to burn sugar may possibly occur within the bodies of these patients, but until such an assumption has been demonstrated by respiration experiments, they will remain examples of ketonurias which apparently do not depend upon carbohydrate starvation.

Ketonuria and Carbohydrate Starvation in Diabetes.—In diabetes also there exists no exact relationship between the degrees of ketonuria and of carbohydrate starvation in different patients. Many exceptions exist to the general rule that the less sugar a diabetic can burn the more marked is his ketonuria. Certain patients with an extremely low tolerance for carbohydrates may show only small amounts of the acetone bodies in the urine, while other patients with a much better tolerance for carbohydrates may show pronounced ketonuria. It would appear, therefore, that while carbohydrate starvation is the most important of the known causes for ketonuria it cannot be regarded as the sole cause, and even where it is the principal or sole cause the degree of ketonuria does not run exactly parallel to the degree of carbohydrate starvation.

Interrelationship of the Acetone Bodies

The intimate chemical relationship which exists between these bodies is readily seen from their structural formulae:

Beta-oxybutyric Acid	Aceto-acetic Acid	Acetone
CH_3	CH_3	CH_3
$CHOH$	CO	CO
CH_2	CH_2	CH_3
$COOH$	$COOH$	

Their intimate physiological relationship is indicated by the fact that they commonly occur together, not only in diabetic coma but in the other metabolic disturbances already enumerated. When only very small amounts are present in the urine, reactions for acetone are most apt to be found; but, as the amounts increase, the ferric chlorid reaction for aceto-acetic acid appears and, finally, evidence of the presence of beta-oxybutyric acid is obtained. The presence of acetone in the urine is, therefore, of less significance than that of aceto-acetic acid, and this in turn is of less significance than the presence of beta-oxybutyric acid. If large amounts of these bodies are present, the quantity of beta-oxybutyric acid usually exceeds that of the other substances. Recent studies by Neubauer, Landergren, and others have shown that in such cases from 60 to 85 per cent of the acetone bodies in the urine are present as beta-oxybutyric acid. Indeed it has been suggested by Gigon, that the amount of beta-oxybutyric acid in the urine of severe cases may be roughly estimated by determining the quantities of acetone and aceto-acetic acid present and multiplying by a factor (4 to 6).

Acetone of Indirect Importance in Diabetic Coma.—We have said that reactions for acetone are relatively common in the urine and it is well known that considerable quantities of acetone may be eliminated in the expired air of patients. It is questionable, however, whether acetone, as such, occurs to any considerable extent in the body. In the urine, aceto-acetic acid readily decomposes into acetone, and Folin, Embden and others have shown that, if care be taken to prevent this decomposition, only very small amounts of acetone are found in the urine. Furthermore, if acetone be given by mouth little is excreted through the kidneys, even though it may be present in the blood in demonstrable quantities. Nearly the whole amount given can be recovered in the expired air. It, therefore, appears that acetone is not readily metabolized even by the normal body, and that it is not readily excreted through the kidneys. The acetone which is present in the expired air of patients suffering from ketonuria may have been derived from the aceto-acetic acid in the blood through chemical changes in the lungs. In view of these facts and of the well-established relatively non-toxic character of acetone, it is certain that no direct importance can be attached to this compound in the production of diabetic coma. Its importance from the clinical standpoint resides in the fact that its recognition suggests the presence of the more important aceto-acetic and beta-oxybutyric acids.

Derivation of the Acetone Bodies

Theoretically it is possible to derive the acetone bodies from carbohydrates, from proteins, or from fats. Physiological studies must be

relied upon, however, for determining which of these possible sources is chiefly responsible for the acetone bodies which occur under physiological or pathological conditions. Acetone, for example, may be prepared in vitro by the fermentation of carbohydrates, but the older view that carbohydrates may be a source of the acetone bodies in the animal body has been definitely abandoned, for the reason that the appearance of these bodies is favored by carbohydrate starvation and may be prevented in certain cases by carbohydrate administration.

Derivation from Proteins.—The accumulated evidence indicates that in the animal body the acetone bodies are derived either from fats alone or from proteins and fats. This evidence is based upon two types of experiments. In the first place, Embden and his coworkers have shown that if the dog's liver be perfused with blood, acetone (or aceto-acetic acid) is formed in fairly constant amounts. When certain substances are added to the perfused blood, the amounts found are increased, apparently because the substances added are converted into acetone (or aceto-acetic acid) in the liver. In the second type of experiment, various substances, fed to men or animals already showing acetone bodies in the urine, have increased the amounts of these bodies. By these methods it has been shown that certain building stones of the protein molecule, and in particular leucin, tyrosin, and phenylalanin, cause an increased formation and elimination of the acetone bodies. While the derivation of acetone bodies from proteins cannot be denied, it is certain that this is not their sole source in diabetes. In certain cases, the amount of acetone bodies is so large that it could not possibly have been derived entirely from the protein metabolized. In a patient described by Magnus-Levy, for example, 342 grams of beta-oxybutyric and aceto-acetic acids were eliminated during three days in addition to what was lost in the expired air; yet the total protein metabolized during this time was but 271 grams. Since considerable sugar (not less than 120 grams) must have been derived from the protein, it was impossible that the proteins burned could have given rise to the large quantity of the acetone bodies found. Obviously they must have been derived mainly from the catabolism of fats. We have seen that in carbohydrate starvation a higher level of protein metabolism tends in general to decrease the elimination of the acetone bodies in the urine, because other products of protein metabolism, and especially glucose, may by their combustion inhibit the formation of these bodies. In very severe diabetes, however, where the sugar derived from proteins is not well burned, a higher level of protein metabolism may be followed by an increased elimination of acetone bodies in the urine. This is shown in the following table taken from von Noorden:

	N in Urine	Sugar	Acetone	Ammonia	Remarks
Wa.......	6.10	7.3	0.58	1.7	Each patient on a carbohydrate free diet
	15.32	82.7	2.14	3.0	
Mi........	9.53	19.1	1.18	2.3	Figures represent averages of three days
	16.62	54.7	2.90	3.4	
Ab........	6.30	5.2	0.42	1.7	
	17.25	60.4	1.76	3.8	

From this table it is evident that where a patient has lost in a large measure the ability to burn the sugar derived from proteins, a higher level of protein metabolism may increase the elimination of the acetone bodies in the urine. It seems probable, therefore, that proteins are a source of limited amounts of the acetone bodies in severe cases of diabetes.

Main Derivation from Fats.—Numerous facts support the view that the acetone bodies are derived in large part from an incomplete combustion of fats. In the first place, quantitative calculations, such as those of Magnus-Levy, indicate that, when very large amounts are excreted, no other source for the total quantities eliminated is possible. In the second place, when a ketonuria is produced in normal individuals by carbohydrate starvation, the ingestion of large quantities of proteins with increased protein catabolism tends to diminish rather than to increase the amount of acetone bodies eliminated. This indicates that, in normal individuals at least, a higher level of nitrogenous catabolism gives rise to more substances which depress, than substances which increase the formation of the acetone bodies. Finally, Forssner has shown that, under proper experimental conditions (carbohydrate starvation, restriction of proteins), the administration of fat may increase the elimination of acetone bodies. In diabetes also the sudden administration of large quantities of fats may increase a preëxisting ketonuria and clinicians are becoming more cautious in prescribing such diets.

Chemistry of Derivation from Fats.—The chemical changes which lead to the formation of acetone bodies from the products of fat combustion in the animal body have been studied by various methods during the past decade. Embden and his coworkers determined the effect of adding various substances to the fluid perfused through the liver, Baer and Blum studied the effect of feeding various chemical substances to diabetic patients and depancreatized dogs, and Ringer made similar observations upon phlorhizinized dogs. By these methods it has been demonstrated that normal fatty acids with four, six, eight, and ten carbon atoms lead to a production of the acetone bodies, whereas normal fatty acids with an uneven number of carbon atoms do not cause such an increase. Since the principal normal fatty acids in the food and in the body (palmitic and stearic acids) possess an even number of carbon atoms, it has been

assumed that, in the normal metabolism of the body, the fatty acids are broken down by the successive splitting off two carbon groups at a time, owing to successive oxidations of the carbon group which occupies the so-called beta position. This conception may be represented by the following general chemical equations:

$$
\begin{array}{ccccc}
CH_3 & & CH_3 & & CH_3 \\
| & & | & & | \\
CH_2 & & CH_2 & & CH_2 \\
| & & | & & | \\
2nCH_2 & & 2nCH_2 & & 2nCH_2 \\
| & & | & & | \\
CH_2 & +O= & CH_2 & +5O= & CH_2 \\
| & & | & & | \\
CH_2 & & CHOH & & COOH \\
| & & | & & \overline{\quad\quad} \\
CH_2 & & CH_2 & & \\
| & & | & & \\
COOH & & COOH & & 2H_2O+2CO_2
\end{array}
$$

In the degradation of the fatty acids, therefore, a succession of simpler acids is formed by oxidation in the beta position and by splitting off two carbon atoms at a time. Eventually butyric acid is reached. This is oxidized in the usual beta position forming beta-oxybutyric acid:

$$CH_3.CH_2.CH_2.COOH + O = CH_3.CHOH.CH_2.COOH.$$

The disturbances which lead to the production of the acetone bodies begin at this point. Either there is a failure to burn beta-oxybutyric acid in the normal manner and this results in an abnormal formation of aceto-acetic acid (and acetone) or else aceto-acetic acid is a step in the normal combustion, but the process is halted at this point. At any rate, it is in this final stage of fat combustion that the difficulty is encountered.

Relation between Fat and Carbohydrate Combustion.—We have seen that this inability to complete the combustion of fats is the most important cause of ketonuria, and that ketonuria is most frequently encountered in deficient carbohydrate metabolism. From these facts the conclusion has been drawn that the final combustion of fats is assisted in some way by the simultaneous combustion of carbohydrates; or, to use a current and more striking expression, that, in the body, fats burn in the flame of the carbohydrate combustion. Like many such expressions, however, this cannot be taken too literally and it must be recognized that other explanations for the observed facts are possible and even more probable. We have seen, for example, that the relation between carbohydrate starvation and ketonuria is by no means a rigid one, and that some types of ketonuria probably do not depend upon a failure to burn carbohydrates at all. It would seem as though the final combustion of fats depends only indirectly

upon carbohydrate metabolism. When the body does not have at hand the full supply of carbohydrates or having it cannot metabolize it, there is necessarily an increase in the combustion of fats and it may well be that the extra strain thrown upon this mechanism by the increased load may lead to disturbance. Or, again, it is possible that the disturbance in carbohydrate metabolism in diabetes is followed by some coincident weakening in the normal capabilities of the body to handle fats and that this contributes to the ketonuria.

The Cause of Diabetic Coma

We have seen that in diabetic coma there is always a marked increase in the acetone bodies excreted in the urine and in the expired air. The amount in the blood is also increased, rising according to Marriott from the normal level of less than 5.5 mg. per 100 cm. of blood to 70 mg. or more. Furthermore, the symptoms of diabetic coma indicate a severe and specific intoxication. The relation of the acetone bodies to this intoxication remains to be discussed. That acetone itself is in no way responsible for the toxic state is certain. It is relatively non-toxic, possessing properties that lie between those of alcohol and chloroform. Possibly it does not occur at all in the body, and certainly the quantities present can produce no serious intoxication.

Acid Intoxication.—The toxic symptoms of diabetic coma are, without doubt, attributable to the occurrence of aceto-acetic and beta-oxybutyric acids in the body. These acids may produce the intoxication either by virtue of their acid qualities, a so-called acid-intoxication, or by virtue of some specific toxic effect produced by their neutral salts. The general features of acid intoxication have already been considered (page 248), and there can be no doubt but that a patient in diabetic coma shows all the classical features of an acid intoxication. The ammonia in the urine is increased, the titratable alkalinity of the blood is diminished, the carbon-dioxid content of the blood is diminished, the tension of CO_2 in the alveolar air is low, the characteristic breathing is that seen in acid intoxication, and the amount of sodium bicarbonate which must be administered in order to make the urine alkaline is far beyond the normal. The acid intoxication theory receives further support from the results of alkaline treatment. Patients who have passed into diabetic coma have frequently been brought out of the coma for varying periods of time by intravenous injections of sodium carbonate solutions. Usually they have lapsed again into unconsciousness, but in some cases the recovery has continued for months and more. Furthermore, if the urine can be kept neutral or alkaline by the administration of sodium bicarbonate, the danger of coma is greatly, if not altogether, averted.

Intoxication by Salts of Ketonic Acids.—On the other hand, there

is clinical as well as experimental evidence that diabetic coma is not entirely an acid intoxication. Patients are said to have passed into coma even during the administration of sufficient quantities of alkalis to keep the urine alkaline. The intravenous injection of alkalis which has frequently brought a comatose patient to consciousness has usually failed to prevent a relapse within hours or days. Direct experimental evidence that the neutralized salts of beta-oxybutyric acid are toxic has been advanced by Wilbur, Ehrmann and others. Indeed the symptom complex produced by the administration of sodium beta-oxybutyrate has many points in common with that of diabetic coma in man. With the present evidences, therefore, it seems probable that while diabetic coma results mainly from an acid intoxication, specific toxic properties of the salts of the ketonic acids may play a part in its pathogenesis.

Pentosuria

The pentoses are carbohydrates which contain five carbon atoms ($C_5H_{10}O_5$). In plants they occur in a combined state in the nucleic acids of nucleoproteins as well as in a state of polymerization, analogous to the ordinary starches.

Traces of pentose may appear in the urines of normal individuals, especially after eating cherries, apples and other vegetable substances.

In chronic pentosuria there is a continual excretion of pentose in the urine which is independent of the character of the diet. The condition frequently occurs in several members of the same family. Some thirty cases have been reported. The origin of this pentose is quite unknown. It has been suggested that it may arise either from the nucleoprotein metabolism or from certain sugars (galactose), but in neither case has the origin been definitely established. Chronic pentosuria produces no symptoms and it is of clinical interest mainly because the urine has mild reducing properties which may lead to a mistaken diagnosis of diabetes.

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Chapter V

The Purin Metabolism—Gout

Gout is characterized by the deposition of sodium monourate in certain tissues of the body. Before discussing the functional disturbances in gout it will, therefore, be necessary to present the current views regarding the normal course of uric acid metabolism in the human being.

Normal Purin Metabolism

Catabolism of Nucleoproteins.—In the normal metabolism of man uric acid and related substances are derived in the main, if not entirely, from the decomposition of nucleoproteins. These latter are found chiefly in the nuclear material of cells, and the uric acid formed in the body, therefore, bears an intimate relationship to the chemical changes which take place in the living cellular substance. The degradation of nucleoproteins takes place in the following manner:

Nucleoprotein

Globulin — Nuclein

Globulin, Histon, etc., — Nucleic acid

According to Jones, there are but two nucleic acids in nature, one obtainable from the nuclei of animal cells and the other from the nuclei of plant cells. In each case the decomposition of the acid yields (1) phosphoric acid; (2) two purin bases, guanin and adenin; (3) pyrimidin derivatives, and (4) a carbohydrate group. While both animal and vegetable nucleic acids contain in common the phosphoric acid, the two purin bases and the pyrimidin derivative cystosin, they differ in that the former yields the pyrimidin derivative thymin while the latter yields uracil, and in that furthermore the former probably contains a hexose carbohydrate group while the latter contains a pentose group. Of interest in the present discussion is the fact that the guanin and adenin present in nucleic acids belong to the group of so-called *purin bodies,* which numbers among its

members the other purin bases, xanthin and hypoxanthin, as well as uric acid.

Sources of the Purin Bodies.—(a) Exogenous Purins.—The purin bodies present in the human organism are derived from two chief sources. The first of these is the food, and purin bodies derived from this source are spoken of as the exogenous purins. The nucleoproteins in the food may be split to the nucleic acid stage during gastric and pancreatic digestion. The nucleic acid itself resists these digestive juices, but a further degradation occurs in the intestines, owing in part to the action of the succus entericus and in part to the action of bacteria. In the intestinal mucosa still further splitting probably takes place with the liberation of purin bases. During the processes of digestion and absorption, therefore, the nucleoproteins taken in the food are decomposed and the purin bodies thus liberated are in part taken up by the body to form the exogenous purins. In part they are decomposed and lost in the intestines.

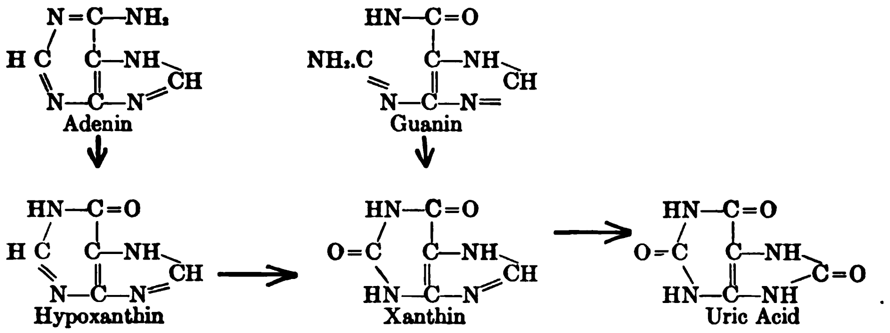
(b) Endogenous Purins. The second source of purin bodies in the animal organism is the decomposition of the nucleoproteins of the tissues. For each individual there seems to be a fairly fixed rate of nucleoprotein catabolism, which varies to some extent, however, with the vital activities of the cells.

There is no doubt but that the animal organism can synthesize nucleoproteins and that it can do this even though it has at hand neither preformed pentose nor preformed purin bodies. In the eggs of birds and insects, for example, nucleoproteins are practically absent; yet during the development of the chick and of insect larvae, these are formed in considerable quantities. The migrating salmon does not take food, yet it forms enormous quantities of nucleoproteins. Finally, milk or other diets which are practically free of purins constitute an adequate food supply over long periods of time. Under such circumstances the body maintains its store of tissue nucleoproteins by synthesizing the necessary carbohydrate and purin bodies and by building these up into the complex nucleoproteins.

Urea.—It is well known that in birds and reptiles uric acid constitutes the chief nitrogenous constituent of the urine and it has been shown that birds synthesize uric acid from urea, ammonium salts or amino acids. Uric acid has also been derived from urea in the laboratory. It was formerly held that such a synthesis occurs in the human body; but it is becoming more and more probable that in man uric acid never represents a further elaboration of the urea waste of the body. It is a specific end-product of the nucleoprotein catabolism.

Conversion of the Purin Bodies.—We have seen that the purin bodies arise mainly from a breaking down of nucleic acid, which is in turn derived from the nucleoproteins of the body or food. The chief purin bases which are formed in this manner are adenin and guanin. The chemical

structure of these bases and the changes which take place when they are converted into other bases and into uric acid are evident from inspection of the following structural formulae.



Two types of chemical processes take place in the conversion of the purin bases into uric acid. The first of these is a deaminization whereby the amino group is removed. This occurs when hypoxanthin is formed from adenin and when xanthin is formed from guanin. The second process is an oxidation. This takes place when hypoxanthin is converted into xanthin and when the latter is converted into uric acid. These chemical conversions are performed by special ferments which are found in certain tissues of the body.

It has been assumed thus far that the decomposition of the nucleic acids with formation of purin bodies is always completed previous to the deaminizations and oxidations which convert the purin bases into uric acid. It is probable, however, that this order is not strictly followed in the body. There is evidence that specialized ferments may cause deaminization while the purin bodies are still combined with the carbohydrate radicle. For example, Jones has shown that watery extracts of all human tissues are unable to deaminize adenin itself although they exert this action upon the adenin held in combination.

In the human body uric acid is the chief end-product of the nucleoprotein metabolism and in human urine it forms by far the largest part of the purin bodies present. In most other mammals, except the anthropoid apes, uric acid does not appear to be the chief end-product of nucleoprotein metabolism. Most of the purin nitrogen in the urine is present in the form of allantoin, a substance which appears in the human urine only in traces. If uric acid be fed to these animals it is eliminated almost entirely as allantoin. It was formerly believed that considerable amounts of uric acid are normally destroyed in the human body by being converted into urea. At the present time, however, there is much doubt and discussion concerning this supposed destruction. Unlike the tissues from many animals, those from man and the anthropoid apes are unable to

decompose uric acid in vitro. Furthermore, when uric acid is fed to man quantities up to one-half or more of that fed can subsequently be recovered from the urine in excess of the normal excretion.. Probably some is lost in the intestines, for when uric acid is injected subcutaneously sixty to ninety per cent may be recovered. It is certain that the amount of uric acid which is destroyed in the human body is much less than was formerly supposed and many believe with Wiechowski that practically none is thus lost. According to this view, the purin bodies of the urine are not only derived solely from the nucleoproteins but the amount excreted in the urine indicates the amount of nucleoprotein metabolism taking place in the body.

Normal Excretion of Uric Acid.—Any determination of the amount of purin bodies excreted in the urine must take into account the two chief sources of these bodies; those which arise from the food, and those which arise during the course of the body metabolism. The latter or endogenous purin bodies are determined by placing the individual upon a purin free diet. When placed upon such a diet, the purin excretion of a given individual is as a rule remarkably constant not only from day to day but even over long periods of time. The endogenous excretion for different individuals, however, varies considerably, the figures ranging from about 0.2 to 0.6 gram daily. Apparently, therefore, different individuals live at different levels of nucleoprotein metabolism, but each maintains his own level with remarkable constancy. Approximately ten per cent of the total amount of purin bodies in the urine consists of the purin bases, the remainder being uric acid.

The amount of exogenous uric acid excreted in the urine is determined by placing the individual upon a purin free diet for several days and in this way estimating his level of endogenous excretion. Having found this level, food containing the precursors of uric acid are fed, and the excess of uric acid appearing in the urine is then determined. By this method it has been shown that when purin-containing foods are given there is a very prompt rise in the excretion of uric acid. This usually lasts not more than one or two days after discontinuing the feeding of purin-containing food. When nucleoproteins are taken by mouth, approximately fifty per cent of the uric acid which could be derived from the food may be recovered from the urine. Larger proportions are recovered if uric acid has been injected subcutaneously. Two explanations have been offered for the portions not recovered: either it has been destroyed in the body or it has been lost in some not yet determined manner.

Nucleoproteins are particularly abundant in those foods which contain a large number of nuclei; especially in sweetbreads (thymus, thyroid), kidney, liver and brain. Compared with these, muscle is relatively poor in purin bodies, but since it is ordinarily consumed in relatively large quantities it is the most important carrier of purins in an ordinary diet.

There is no difference in this particular between the red and white meats. Most vegetables are poor in nucleoproteins and this is especially true of those which grow under ground. The leguminous vegetables, peas and beans, are, however, relatively rich in these substances. In choosing a low purin diet, therefore, the chief reliance must be placed upon such foods as milk, bread, eggs, starches, cream and butter.

Tea, coffee and cocoa contain caffein and similar substances which are methyl substitution products of the purin ring. Although these substances are changed in the body they are not converted into uric acid but are excreted as other simpler methyl purins.

Increase Purin Metabolism

The endogenous purin metabolism is increased in all conditions where there is destruction of cells in the body. In leukemia, in resolving pneumonia, in septic processes and in acute degenerations of the liver there is an excessive destruction of cells with liberation of nucleoproteins and excretion of unusually large quantities of endogenous uric acid. The amount of uric acid in the blood in these conditions and particularly in leukemia is often remarkably high. In the latter disease the uric acid excretion may be increased by exposing the patient to the action of the x-rays, owing to the destructive effect which these rays exercise upon the abnormal cells in the blood and tissues.

The Purin Metabolism in Gout

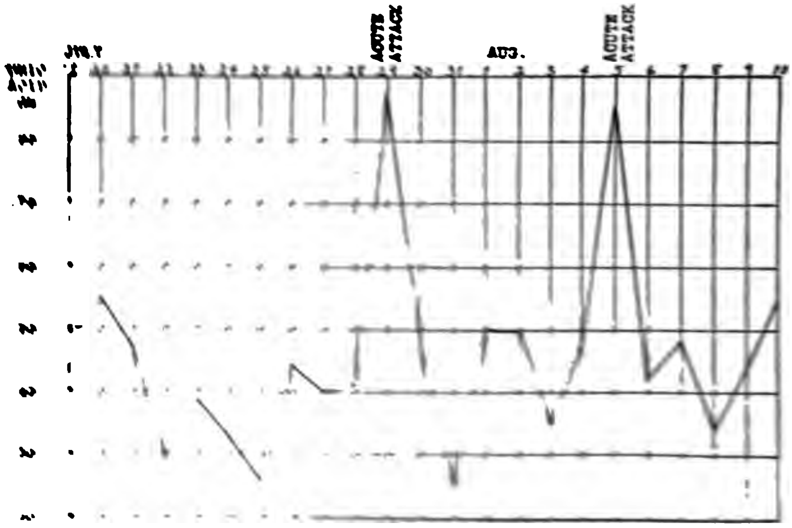
Etiology of Gout.—The exact causes which lead to gout and to the disturbed purin metabolism seen in this disease are not well understood. Beyond doubt there is an *hereditary tendency* to the disease which is transmitted to the descendants of certain families. Among the acquired factors which predispose to gout are an habitual *overconsumption of food* and especially of meats. The continual ingestion of considerable quantities of purin-containing foods burdens the normal body mechanism for handling the uric acid derived from this source and favors the development of gout in those in whom this mechanism is already weak. A *sedentary life* with little exercise also favors the development of gout. It is for these reasons that gout is particularly apt to occur in those belonging to the leisure classes, who live well and take but little exercise.

Certain chronic intoxications also diminish the ability of the body to handle the purin metabolism in the normal manner. *Alcoholism* in particular and especially the long-continued use of malt liquors distinctly favors the gouty tendency. Chronic alcoholism is the most important

cause of gout in the lower social classes. *Chronic lead poisoning* is also an important predisposing cause of gout.

Gout shows many interesting relationships to metabolic and other diseases. Not infrequently the gouty patient himself suffers from these other diseases. Again in gouty families there may be an unusual tendency not only toward the development of gout but toward the development of those closely related conditions. This general tendency is often spoken of as a *gouty diathesis*. The most important of the diseases which tend to be associated with gout are diabetes, obesity, cardiac and cerebral arteriosclerosis, chronic hypertension, chronic interstitial nephritis, certain skin diseases, digestive disturbances, etc. The relationship of these various conditions to true gout is at the present time obscure. Some are unusual manifestations of gout itself, so-called irregular gout. Others, especially the kidney lesions, may be factors in the causation of gout. In still other cases, as in obesity and diabetes, the disturbance in purin metabolism tends to be associated with other metabolic disorders.

Uric Acid Excretion in Gout.—(a) Endogenous Uric Acid.—We have seen that when normal individuals are placed upon a purin free diet the uric acid excretion is relatively constant for a given individual,



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approaches the lower level of the normal limits and in some it may be distinctly below the normal minimum. On the other hand, certain cases which ought perhaps to be grouped separately show an unusually high uric acid output.

The acute paroxysms of gout are at times associated with changes in the endogenous uric acid excretion. There may be a fall just before the onset of the attack; but during and just after the attack there may be a distinct increase in the uric acid output which may in turn be followed by a slight drop beneath the normal. Such variations are shown in the accompanying figure which has been constructed from the determinations of R. Köster. In many cases of gout, on the other hand, no change of uric acid excretion has been observed during the acute paroxysms (see, for example, Daniels and McCrudden).

(b) Exogenous Uric Acid.—When uric acid or its precursors are administered to gouty patients the resulting excretion of exogenous uric acid usually but not invariably shows deviations from the normal. As compared with normal individuals, gouty patients excrete the excess of uric acid formed from articles in the diet more slowly. In place of completing the excretion of a single purin-containing meal within one or two days slight excesses may appear in the urine for three, four or more days. The total excreted may also be diminished. The output under such circumstances does not show the sharp and brief rise in uric acid excretion which characterizes the normal. Similar differences have been described when uric acid has been injected intravenously. In some cases of gout only twenty per cent or less of the injected material has been recovered whereas in the normal individual from 60 to 90 per cent are recovered. It has been proposed to utilize these variations from the normal for diagnostic purposes, but up to the present they have found no wide practical application. Not only do they require a careful metabolic technic but the changes here described do not seem to be pathognomonic. Occasionally normal individuals show a prolonged excretion of exogenous uric acid while certain gouty patients show normal powers of excretion.

Uric Acid in the Blood.—Numerous recent studies of the uric acid content of the blood in normal and in pathological conditions have confirmed the old view of Garrod that there is a definite increase in the blood of most gouty patients. This increase has been particularly constant in chronic cases of long duration. It persists even when the patient is placed on a purin free diet. It may be present between the paroxysms of acute gout but here the increase is less constant, especially in early cases. According to the recent work of Folin and Denis the uric acid content of the blood of normal individuals on mixed diets shows an average of 1.8 mg. per hundred c.c. of blood. Definite increases have been found not only in chronic gout, but also in chronic lead poisoning, arterial hypertension, leukemia and other conditions.

Uric Acid in Human Blood

(Expressed in mg. uric acid to 100 gms. blood)

	Non-protein Nitrogen Average	*Urea Nitrogen Average*	*Uric Acid*	
			Average	*Extremes*
21 unselected individuals on mixed diets #	36	20	1.8	0.8–3.0
15 normals on purin free diet°..........	..	..	1.4	0.5–2.9
11 observations on nephritic blood # ...	50	26	2.2	1.0–3.9
12 patients with gout #	33	..	4.3	3.1–5.4
2 patients with leukemia #	..	..	3.6	3.1–4.1
2 cases of lead poisoning #	51	31	4.7	4.7–4.8
4 cases of "uremia" #	231	..	8.4	6.6–10.0

From Folin and Denis.
° From McLester.

It may be seen from this table that the amount of uric acid in the blood bears no definite relation to the amount of total non-protein nitrogen. In gout the increase in uric acid is, as a rule, unassociated with any marked increase in the non-protein nitrogen. In nephritis, on the other hand, there is not infrequently an increase of non-protein nitrogen in the blood with approximately normal amounts of uric acid. When during the late stages of nephritis the accumulation of non-protein nitrogen becomes extreme, however, there is, as a rule, a very marked increase in the concentration of uric acid in the blood which may be greater than that found in gout. In certain cases of gout, furthermore, there appears to be no increase of uric acid in the blood (Daniels and McCrudden).

The uric acid of the blood is probably present almost entirely in the form of monosodium urate. The hypothetical quadriurate of Roberts has received no confirmation. Minkowski has suggested that uric acid may exist in the blood not as the free monosodium salt but in combination with other organic substances and Frank has advanced the hypothesis that nucleic acid or some of its immediate derivatives may be carriers of the uric acid group in the blood. Proof of such an hypothesis has not been furnished but like the similar hypothesis relating to blood sugar it is difficult to disprove. The weight of evidence at present favors the view that the uric acid in the blood is present almost entirely in the form of the free monosodium salt.

Inasmuch as deposits of monosodium urate in the tissues constitute one of the most characteristic features of gout great importance is attached to the question of the solubility of monosodium urate in the blood. The

older view of Klemperer that the blood serum of gouty patients was far from being saturated with uric acid has been called more and more into question within recent years. In the first place we are dealing in the animal body not with uric acid but with its monosodium salt and it has been shown that the latter is less soluble in blood serum than is the former. Gudzent believes that this urate occurs in two isomeric forms which he has identified with the so-called laktam and laktim forms of Emil Fischer. It is believed that the more soluble laktam salt is formed first in the body and that this is changed gradually into the more stable and relatively insoluble laktim salt. Gudzent tested the solubility of the latter salt in a solution which corresponded in its salt content to the blood and found it soluble up to a concentration of 8.3 mg. in 100 c.c. Bechhold and Ziegler believe that the serum-albumin of the blood depresses the solubility of the urates still further and place the solubility of monosodium urate at 2.5 mg. per 100 c.c. A comparison of these recent determinations of the solubility of sodium urate with the amounts actually found in human blood indicates that in gout as well as in certain other conditions the concentration of urates in the blood has reached or has passed the saturation point. It is evident, therefore, that we have here a possible explanation for the deposition of uric acid salts in the tissues of gouty individuals.

The uric acid concentration in the blood is also increased in other diseases than gout. In some of these conditions and in particular in chronic lead poisoning, chronic arterial hypertension and chronic nephritis it is quite possible that we are at times dealing with patients who have irregular gout with urate deposits. In many of these patients, however, as well as in conditions of increased purin metabolism, especially leukemia, it is difficult to explain why the prolonged increase in the concentration of uric acid in the blood does not lead to a deposition of urates in the tissues. Possibly in these cases the uric acid is present in some soluble form such as the laktam salt whereas in gout it is present as the relatively insoluble laktim salt.

Local Deposits of Urates.—It is well known that deposits of monosodium urate occur particularly in certain tissues, such as the cartilages, joint capsules, tendons, muscles and skin. Cartilage appears to have a peculiar affinity for sodium urate. When thin pieces of cartilage are suspended in dilute urate solutions the cartilage absorbs urate in considerable quantity and crystallized deposits may occur in the tissue. After injections of large quantities of uric acid into the peritoneal cavity of rabbits it has been found that this can be demonstrated in the cartilages but not in the other tissues. The older view of Ebstein that the deposition of urates occurred only in necrotic tissue has thus been definitely disproved. Indeed the histological picture of a gouty tophus can be reproduced by the injection of monosodium urate beneath the skin.

Cause of the Acute Attack.—The deposition of urates in the cartilages

or other tissues of the body cause a certain amount of reactive inflammation similar to that which surrounds foreign bodies in general. In many cases the urate deposits produce no symptoms, in other cases they may produce slight pain and more or less marked deformity. The relation of the urate deposits to the typical attacks of acute gout is by no means well understood. It is true that many facts indicate that acute attacks of gout are associated with sudden disturbances in the uric acid metabolism in the body. There is at times a depression in the excretion of endogenous uric acid preceding the attack and an increase in its excretion with or shortly after the acute symptoms. Acute attacks have followed the ingestion of unusual quantities of purin-containing food, and the intravenous injection of uric acid. They have occurred when the endogenous uric acid has been increased suddenly as by exposure to the x-ray or during the resolution of a pneumonia. Finally, attacks of gout have been cut short by the use of atophan which, as we shall see, causes a marked fall in the level of uric acid in the blood.

It seems evident from these facts that the acute gouty paroxysm is intimately related with sudden disturbances in the uric acid metabolism and particularly with conditions which increase uric acid in the body. The exact cause of the paroxysm, however, is not understood. Whether a rapid deposit of uric acid in the joints sets up an acute inflammatory reaction, whether a sudden solution of previously deposited inert urates produces the acute changes, or whether other factors more or less remotely connected with the urate deposits cause the local inflammation and mobilization of urates are questions which have not been settled.

The Effect of Atophan.—Atophan is the trade name given to the chemical phenyl-quinolin-carboxylic acid. This drug exerts a remarkable influence upon the purin metabolism. Following its administration in therapeutic doses there is a striking increase in the elimination of endogenous uric acid, and this is true in gouty as well as in normal individuals. If the administration is continued the increased elimination which is most marked on the first day rapidly diminishes and in normal individuals subsides within a day or two to nearly the normal. In gouty patients, however, the increased elimination of endogenous uric acid may continue much longer and Weintraud and others have observed a diminution in the size of visible tophi during the long-continued use of atophan. When uric acid is injected intravenously either into normal or gouty subjects it is eliminated more promptly and more completely when atophan is given simultaneously. Given during an acute attack of gout it frequently relieves the pain and the acute symptoms very promptly. Folin and Lyman, as well as McLester, have shown that the administration of atophan causes a marked diminution in the concentration of uric acid in the blood at the same time that it causes an increase of uric acid in the urine (See Fig. 68.) It is evident from these observations that the

increased output of uric acid produced by this drug is due, not to an increased formation or liberation of uric acid in the body, but to a more complete and perfect elimination through the kidneys of the acid present in the blood. This reduction of the concentration in the blood probably accounts for the reported reductions in the size of tophi in certain patients, for a lower concentration in the blood would favor the solution of deposits. This action of atophan is relatively specific and it is not necessarily asso-

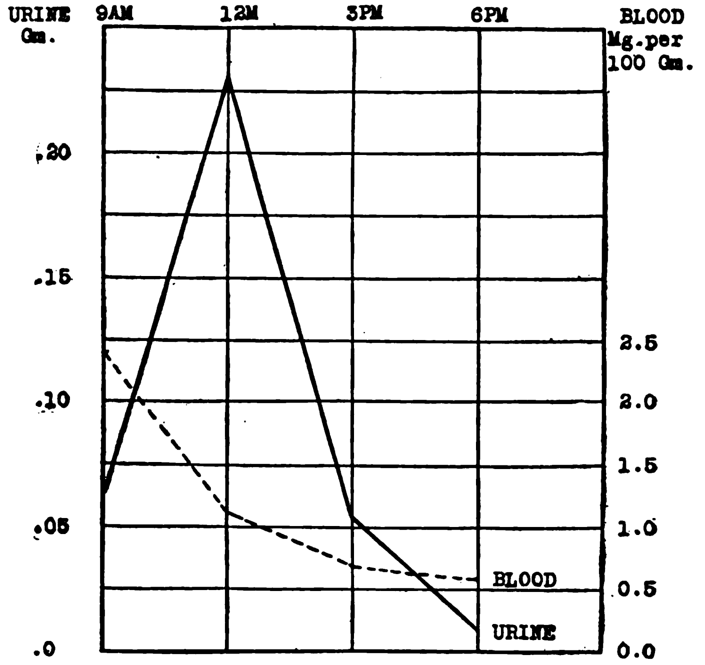

Fig. 68.—Effect of Administration of 3 gm. Atophan at 9 A.M. on the Uric Acid in the Urine and Blood. Note that the Increased Excretion Was Associated with a Diminution in the Blood But that Later the Excretion Fell Below Normal. (From McLester, Arch. Int. Med.)

ciated with any correspondingly great increase in the elimination of other urinary constituents.

Theory of Gout.—In seeking for an explanation of the urate deposits which characterize gout, the most important point which has come into view from modern studies is the fact that in nearly all cases of gout there is an increase in the concentration of uric acid in the blood. We have seen that this increase may in all probability pass the saturation point of the lactic salt in blood serum and that this furnishes a possible explanation for the deposition of urates in the tissues. The cause of this increased concentration of uric acid in the blood may be, on the one hand, an overproduction of uric acid in the body or, on the other,

an insufficient destruction or removal of the uric acid present. We have no reason to believe that an overproduction of uric acid plays any considerable part in the majority of cases of gout. Apparently the body has no source for its uric acid other than the food and the catabolism of its nucleoproteins, and there is no evidence of an increased nucleoprotein metabolism in gouty patients. Their elimination of endogenous uric acid in the urine is as a rule normal or subnormal. Only in occasional cases does the elimination of endogenous uric acid in the urine approach or exceed the upper limit of normal. In such cases Brugsch believes that the gout may be of a peculiar type and in part dependent upon the increased purin metabolism. In the great majority of gouty patients the increase of uric acid in the blood must be attributed to a diminished destruction or elimination rather than to an overproduction of the purin bodies. It is probable that the human body is normally incapable of destroying much uric acid. If one accepts the views of Wiechowski that practically none is destroyed normally, then a failure to destroy could play no part in the etiology of gout. If, on the other hand, one assumes that the normal individual ordinarily destroys a certain proportion of the uric acid formed in his body then a failure to effect this destruction might be one cause of the disturbance of metabolism present in gouty patients. It is difficult to disprove this hypothesis.

On the other hand, more and more evidence is accumulating in favor of the view that gouty patients show a specific limitation in their ability to excrete uric acid. This is plainly indicated by the fact that in gout the level of uric acid in the blood is distinctly higher than normal and yet the excretion into the urine is normal or subnormal. The cause of this specific inability may lie either in the kidneys or in the blood itself. Some years ago Minkowski advanced the view that uric acid might be present in the blood of gouty patients in combination with other substances and that these combinations might be such that they could not be excreted by the kidney. Up to the present, however, definite proof of such a combination has not been brought and it seems on the whole more probable that the difficulty in excretion lies in the kidneys themselves. Just what is the nature of the difficulty is difficult to say. It is certainly not necessary to assume that a definite threshold must be reached before the kidneys begin to excrete uric acid, and that when this threshold is reached excretion takes place normally. The condition may be comparable to the nitrogenous retention present in certain cases of chronic nephritis where an increased concentration of urea in the blood seems necessary in order that the kidney may excrete the usual amount of urea. We know from the study of nephritis that the excretory functions of the kidney are highly specialized. Certain patients may show nitrogenous retention while excreting chlorids and water with ease while others excrete nitrogenous waste readily but show a marked insufficiency toward the excretion of salt and

water. It is not improbable that in still other patients there may be a specific inability on the part of the kidneys to excrete uric acid and that this may constitute one essential disturbance in gout. That it is not the sole disturbance, however, is indicated, first by the fact that the level of uric acid in the blood may be high in leukemia and in nephritis without the occurrence of gouty manifestations and, second, that attacks of acute gout may occasionally occur when the level in the blood is low. Variations in the solubility of the acid in the blood or changes in the tissues may account for these discrepancies but of these we know almost nothing and the final cause of gout therefore still awaits solution.

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Chapter VI

Diseases of the Liver and Pancreas

Functions of the Liver

No organ in the body possesses such a variety of functions as the liver. Its portal circulation brings it into intimate relationship with the gastro-intestinal canal and spleen, and any blood changes occurring in these organs must act with particular intensity upon the liver. Especially important is the fact that all the material which enters the blood from the stomach, the small intestines and the proximal portion of the large intestines must pass through the liver before it is permitted to reach the general circulation.

This passage through the liver helps to protect the body from various toxic substances which may be absorbed from the alimentary canal. Some are converted directly into non-toxic compounds, as when ammonium salts are converted into urea. Some are combined with glycocoll, sulphuric acid, or glycuronic acid and are, thereby, deprived of their poisonous properties, as happens in the case of phenol and similar compounds. Lastly, alkaloidal and mineral poisons are, to a certain extent, removed from the blood during their passage through the liver.

The liver also plays an important part in carbohydrate metabolism. It is the most important of the organs which remove an excess of sugar from the blood, store it in the form of glycogen and give it back to the body when it is needed. The liver is one site of important changes in the intermediary nitrogenous metabolism. It contributes fibrinogen to the blood. It plays an important rôle in anaphylactic shock. Finally, it secretes bile, which, as we have seen, assists the intestinal digestion and absorption of fats.

Many disturbances of these liver functions are discussed elsewhere under the appropriate headings. We shall consider here, first, disturbances in the secretion of bile, and later, certain other functional disturbances which have been used as tests of hepatic disease.

Disturbances in the Secretion of Bile

Important Constituents of the Bile

The bile contains three important and characteristic groups of compounds: the bile pigments, the bile salts, and fatty materials, particularly cholesterin.

Bile Pigments

The bile pigments are products of hemoglobin catabolism. When hemoglobin is decomposed, there are formed a protein, called globin, and a relatively simple iron-containing compound, called hematin. Although the protein makes up about 94 per cent of the hemoglobin molecule, it is the hematin complex which gives to hemoglobin its peculiar properties of color and of being an oxygen-carrier. The carrying of oxygen is intimately associated with the iron content of the hemoglobin. The property of color, on the other hand, is independent of the iron content, for a series of colored compounds may be formed from hematin after the iron has been removed. Among these are the bile pigments. That these pigments are formed in the body from hemoglobin metabolism has been repeatedly demonstrated. The amounts formed are increased when pure hemoglobin is injected into the blood stream, or when an excessive amount of hemoglobin is liberated by an abnormal destruction of the red blood corpuscles in the body.

Extrahepatic Formation of Bile Pigments.—The conversion of hemoglobin into bile pigment takes place chiefly in the liver, and when the erythrocytic destruction is excessive, there is not only an increased formation of bile pigments but iron-containing compounds are deposited in the liver. That the conversion of hemoglobin into bile pigment may also occur outside of the liver is evident from the fact that old extravasations of blood frequently contain pigments which are identical with bilirubin. Whether the conversion of hemoglobin into bile pigments ever occurs outside of the liver in sufficient quantity and with sufficient speed to give rise to a general icteric staining of the body has been much discussed, but it now seems to have been answered in the positive sense. Whipple and Hooper have shown that when hemoglobin is injected into the circulating blood of dogs it is rapidly converted into bile pigments, even though the liver has been eliminated from the circulation.

Conversion of Bile Pigments into Urobilin.—The fate of the bile pigments which pass from the liver into the intestines is in part known. The larger portion is reduced to urobilinogen or urobilin. Some of the latter is lost in the stools, while some is taken up by the intestinal mucosa and is carried in the portal circulation back to the liver, where it may be reëxcreted in the bile either as such or possibly after reconversion into the

ordinary bile pigments. Under certain conditions a considerable amount of urobilinogen that has been resorbed from the intestines passes through the liver into the general circulation and is excreted by the kidneys.

Pathological Variations in Quantity.—Pathological variations in the quantity of bile pigments secreted by the liver depend primarily upon pathological variations in the rate at which red corpuscles are destroyed. The amount of urobilin and urobilinogen found in the stools and in the urine has, therefore, been used as a rough measure of the rate of red cell disintegration in the body, and the important bearing of such studies upon our conception of certain anemias and other blood conditions will be discussed elsewhere.

Bile Salts

The bile salts are salts of glycocholic and taurocholic acids. These acids are composed of a common element, cholic acid, which is combined with glycocoll and taurin respectively. Glycocoll and taurin are derivatives of protein metabolism. Glycocoll is an amino acid which is a common protein-building stone, and taurin is closely related to cystin, which is a sulphur-containing product of protein decomposition. Concerning the origin of the characteristic component of the bile salts, viz., cholic acid, we know practically nothing.

Circulation of Bile Salts.—The bile salts which have reached the intestines and have there played their part in the digestion and absorption of fats, are taken up by the mucous membrane, carried back to the liver in the portal blood stream and again excreted in the bile. Comparatively small amounts are lost in the stools. There is thus a continual circulation of the bile salts between the liver and the intestines and the necessity for their new formation is reduced to a minimum.

Cholesterin

Cholesterin, another important constituent of the bile, has a wide distribution in the animal body, being found in considerable quantity in the central nervous system, in the adrenal cortex, the thymus and the ovaries. Pathological deposits also occur. Aside from the cholesterin taken in the food, but little is known of its origin. Its presence in gall-stones makes it a compound of particular interest in discussing the functions of the liver and of its excretory ducts.

Jaundice

By jaundice is meant a yellow or greenish yellow staining of the body with bile pigments. On physical examination, this change in color is visible in the conjunctivae, and is particularly evident in the covered parts of the skin which normally show little color from skin pigments or hyper-

emia of the cutaneous vessels. During jaundice the bile pigments are usually excreted in the urine, so that the latter assumes a deep red color, stains the garments, and gives the usual tests for bile pigment. In certain types of jaundice, however, particularly chronic hemolytic jaundice and the physiological jaundice of the new born, bile pigments may not be found in the urine. The bile pigments may also be excreted in the sweat. As a rule they do not appear in the tears, saliva or sputum, unless these contain inflammatory products. A retention of the other characteristic biliary constituents, i. e., bile salts and cholesterin, may or may not be demonstrable in jaundice.

Obstructive Jaundice

The best understood type of jaundice is that which is caused by a gross mechanical obstruction of the common bile duct or of the hepatic duct. Such an obstruction may be caused by malignant new growths, by impacted gall-stones, by cicatricial stricture of the ducts, or by pressure or kinking from inflammatory adhesions. Gross mechanical obstructions of the bile ducts may also occur within the liver. As a result of such obstructions the bile ducts become dilated with fluid. They are filled at first with colored bile, which may later give place to colorless fluid that is probably secreted by the bile passages. The bile capillaries in the liver are dilated and may rupture. The components of the bile are absorbed in the liver and pass into the body fluids. Whether this absorption takes place mainly through the lymphatics or through the blood capillaries does not seem to have been definitely settled.

The length of time which must elapse before a complete obstruction of the common bile duct in man gives rise to the clinical signs of jaundice has been estimated by Eppinger at about forty-eight hours. Obstructive jaundice is associated with a demonstrable accumulation of bile pigments and of cholesterin in the blood, and with an excretion of bile pigments and salts in the urine.

Extensive Hepatic Necrosis Rare in Man.—In guinea-pigs obstructive havior of different animals seem to lie in the fact that in those animals such as the dog and man, are but little inconvenienced by obstructive jaundice. They may be said to die from the cause of the jaundice rather than from the jaundice itself. The reason for this difference in the behavior of different animals seems to lie in the fact that in those animals which die early the jaundice is associated with necrosis of the parenchyma of the liver. Only rarely does an extensive necrosis occur in man as the result of obstructive jaundice, and in such cases it may also be associated with the serious symptoms, which will be discussed later (cholemia).

Clay-colored Stools.—It has commonly been held that the characteristic clay-colored stools seen in certain forms of jaundice are conclusive evidence of total exclusion of bile from the intestines. There are reasons,

however, for believing that this is not the only cause of such a decolorization, and that the latter may be brought about by decolorization of bile pigment that has entered the intestines.

Excretion of Urobilin and Urobilinogen.—When the bile pigments are completely shut off from the intestines, urobilin and urobilinogen do not ordinarily appear in the urine; a fact that indicates that these substances are not formed in any quantity unless the bile pigments have access to the intestines. As an obstructive jaundice is clearing up, however, large quantities of these substances may appear in the urine, on account of the excessive quantity of pigments which are then excreted into the intestines from the bile laden body.

Hemolytic Jaundice

We have seen that the bile pigments are derived from the disintegration of hemoglobin and that in conditions of increased hemoglobin catabolism there is an increased formation of these pigments. This has been repeatedly demonstrated by injecting hemoglobin into the circulation of animals. Following a large injection there is a hemoglobinemia, a hemoglobinuria, and an increased secretion of pigments in the bile. An increase of bile pigments in the blood serum and urine is also demonstrable, though this may not be sufficient to produce jaundice in the clinical sense (Yorke and Nauss).

"Hematogenous" and "Hepatogenous" Jaundice.—In the earlier literature the occurrence of "hematogenous," as contrasted with "hepatogenous" jaundice, was frequently attributed to a conversion of disintegrating hemoglobin into bile pigments outside of the liver. The classical experiments of Minkowski and Naunyn showed, however, that in a certain type of jaundice usually regarded as hematogenous, viz., that produced in geese and ducks by arseniureted hydrogen, the liver was an essential factor in the production of the bile pigments; for when this organ was removed no jaundice followed the poisoning. These experiments, coupled with the fact that in cases of supposed hematogenous jaundice in man, bile salts as well as pigments were at times found in the urine, led to the belief that the liver is always an essential factor in the production of jaundice during increased blood destruction. Whipple and Hooper have recently shown, however, that bile pigments may be formed rapidly and in considerable amounts outside of the liver, so that it is possible that a true hematogenous jaundice in the older sense may occur. However this may be, the jaundice following hemoglobin injections is caused by the fact that bile pigments are formed so rapidly, either in the liver or elsewhere, that their immediate excretion by the hepatic cells is not possible.

In Acute Hemolysis.—Jaundice frequently accompanies or follows conditions of acute hemolysis, such as occur, for example, in paroxysmal hemoglobinuria, blackwater fever, poisoning with hemolytic substances,

etc. (See Hemolysis). One important factor in its production is the sudden formation of unusual quantities of bile pigments from the liberated hemoglobin, which throws an unusual strain upon the liver and its excretory ducts. The relation between the degree of hemolysis and the depth of the resulting jaundice is not, however, a simple one. In paroxysmal hemoglobinuria, for example, jaundice is usually far less marked than in blackwater fever. Again, the injection of hemoglobin into the circulating blood of animals produces much less jaundice than when certain hemolytic agents, such as arseniureted hydrogen or toluylendiamin, are used. The relatively marked jaundice in certain forms of acute hemolysis seems due to simultaneous changes in the liver cells or the bile capillaries which lessen their ability to rid the body of the excess of bile pigments present. The nature of these changes in the liver is not well understood, although it is probable that they are very similar to those present in the infectious type of jaundice which will be discussed below.

In Anemia. Chronic Hemolytic Jaundice.—In certain forms of chronic anemia there is an increased rate of hemolysis, and this doubtlessly plays a part in the pathogenesis of the slight jaundice that is not uncommen in chronic hemolytic anemias, of which pernicious anemia may be taken as the type. Here again, however, changes in the liver doubtlessly play a part in producing the jaundice. The most remarkable type of chronic excessive hemolysis is that seen in the rare condition known as chronic hemolytic jaundice, which may occur as a congenital or acquired affection. The erythrocytes of such patients show evidence of rapid regeneration, while examination of the stools and urine shows that the urobilin output may be increased to as much as twenty times the normal. Although the blood serum contains bilirubin, the urine ordinarily contains no bile pigments but only excessive amounts of their derivatives, urobilin and urobilinogen. At autopsy the liver and bile passages show no evidence of diseases other than what is caused by the increased hemolysis. In this type of jaundice there is no retention of bile salts or of cholesterin in the body. The jaundice appears to be due solely to the increased rate of red cell destruction.

Infectious Jaundice

Not infrequently jaundice complicates some well-defined infectious disease, such as pneumonia or general sepsis. There is also a disease, evidently of an infectious character, which is characterized chiefly by the occurrence of jaundice. It ordinarily begins with the usual phenomena of an infectious fever. After a few days jaundice appears, the liver may become swollen and not infrequently some evidence of nephritis is added to the clinical picture. Such cases usually terminate favorably. The infectious symptoms disappear after a few days, while the jaundice may last for a week or more. In other and much less common cases the symp-

toms become more serious and the disease may end fatally. To these more serious types of infectious jaundice the name of Weil's disease has been given. The milder cases are frequently diagnosed as catarrhal jaundice, but whether all cases of so-called catarrhal jaundice are to be classed as mild forms of infectious jaundice is still uncertain. That there is no essential difference between severe infectious jaundice and many cases of so-called catarrhal jaundice is rendered probable from the fact that, when the disease has been observed in epidemics, all grades of the affection may be present.

Obstruction of Common Bile Duct.—In infectious jaundice the stools may be of a normal color or they may be decolorized. The clay color so commonly seen in cases of "catarrhal jaundice" has been held to support the older view of Virchow that in these cases the jaundice is produced by an obstruction of the larger bile ducts, either by a swelling of their mucous membranes or by an obstructive plug of mucus. In very mild cases autopsies are uncommon, and few observations have, therefore, been made which support the view that there is an obstruction in the common duct. It has been noted repeatedly, however, that in the more severe types of infectious jaundice the gall-bladder and the larger bile passages may contain a colorless secretion, and that there is no obvious mechanical obstruction in the larger ducts. Whether the lack of color is caused by a conversion of bile pigments into colorless substances, or whether no bile pigments enter the ducts from the liver, is not altogether clear. It is evident, however, that in this type of jaundice the immediate cause of the clay-colored stools is rarely, if ever, an obstruction of the large bile ducts.

Obstruction of Bile Capillaries.—When, as frequently happens, no obstruction in the larger bile passages can be demonstrated, the cause of infectious jaundice must be sought in the liver itself. Two explanations have been offered to account for this form of jaundice. According to the one, there is a widespread obstruction of the finer bile capillaries in the liver. According to the other, there is a diseased condition of the hepatic cells themselves. Anatomical evidences in favor of the first view have been brought forward, particularly by Eppinger, who found that in infectious, as well as in related types of jaundice due to certain poisons, the finer bile capillaries are often blocked by small casts or thrombi, and that behind the tiny obstructions there are dilatations of the bile capillaries.

Damage to the Hepatic Cells.—On the other hand, there is considerable evidence of a physiological character in favor of the view that the liver cells themselves are damaged in the infectious type of jaundice. The casts described by Eppinger seem to depend upon changes in the character of the bile, and these changes may in turn depend upon an abnormal secretory activity of the liver cells. In the second place, Lemierre, Brulé and their coworkers have demonstrated that, at certain stages of infectious jaundice, there may be a retention of bile pigments (jaun-

dice with [illegible] bile salts into the intestines, as shown [illegible] alimentary [illegible]. In other stages a [illegible] salts, as shown by the [illegible] of alimentary lipemia, may be associated with a [illegible] into the intestines. Such a [illegible] the hepatic [illegible] with the conditions in [illegible], where the [illegible] of nitrogenous wastes may be separately affected. [illegible] evidence of damage to the liver cells in case of [illegible] numerous observations that functional tests [illegible] indicate a disturbed function of the hepatic cells. [illegible] Alimentary Galactosuria. Inasmuch as these [illegible] deviation from the normal during [illegible] that in "catarrhal" jaundice the hepatic [illegible]. It matters little whether this [illegible] the immediate cause of the jaundice, or whether [illegible] obstruction of the finer capillaries. [illegible] jaundice is associated with changes in the [illegible]

Jaundice in Organic Liver Diseases

[illegible] of the liver. In [illegible] the bile ducts [illegible] neoplasms [illegible] may show [illegible] compression or [illegible], and the [illegible] by pyruvic [illegible] urobilinuria. [illegible] other functional [illegible] and [illegible] to the [illegible] this type might [illegible] of the liver may [illegible] secretion [illegible] pressure or by the [illegible]

[illegible] Neonatorum

[illegible] of life that it may [illegible] slight grades of [illegible] occurs in about [illegible] appears on the second [illegible] about the fourth day.

and gradually disappears after a week or more. Icterus neonatorum is peculiar in that bile pigments, though demonstrable in the blood, are not usually secreted into the urine.

Relation to Bile Secretion.—No form of jaundice has given rise to a wider range of speculation than has this physiological type, and yet few facts concerning its pathogenesis are definitely established. That it is not due to a gross obstruction of the common bile duct has been definitely proven by Hess' examinations of the duodenal contents. This investigator found that the duodenal contents of newborn infants practically never contain bile during the first twelve hours of life. During the subsequent twenty-four hours the secretion of bile is variable, but infants who later develop marked jaundice usually show a marked and early discharge of bile into the duodenum. The secretion of bile normally becomes established during the first week or ten days of life, but in general it is more marked in those infants who show decided jaundice. Icterus neonatorum seems, therefore, to be definitely associated with an early and abundant formation of the bile pigments. For some reason these are not freely excreted and jaundice results.

Just what causes this abundant formation of bile pigments in certain infants does not seem to be clear. Possibly, as some have held, there is a physiological destruction of red corpuscles shortly after birth and if this be excessive, jaundice results. This view has recently been upheld by Heimann.

Symptoms of Jaundice

Of the varied symptoms which may occur in jaundiced patients, many are doubtlessly due, not to the retention of bile constituents in the body, but to the primary causes of the jaundice itself or to a coincident injury of the hepatic cells. Malignant tumors, increased hemolysis, and inflammatory processes in the bile ducts frequently complicate the clinical picture. In addition, there are the cases in which serious toxic symptoms arise and which have often been spoken of as cholemia. These "cholemic" symptoms are apparently not due to the retention of bile constituents but to functional changes in the hepatic cells.

Effects Produced by Bile Constituents.—Indeed, surprisingly few manifestations can be directly attributed to the retention of bile constituents within the body. Slowing of the pulse is observed at times and it is believed by many, and particularly by the French school, to be caused by some action of the retained bile salts. The experiments of Stewart and King, however, indicate that the slowing of the pulse is due to the bile pigments which act by increasing the tone of the vagus nerve. The marked itching which annoys certain patients with jaundice is attributed to the action of the bile salts. The occurrence of xanthomata in chronic jaundice has become of increased interest, since it has been shown that

these yellow skin tumors contain cholesterin deposits, and that the blood of patients with obstructive jaundice commonly contains excessive quantities of cholesterin, evidently because this bile constituent is retained in the body.

Functional Disturbances of the Hepatic Cells

We have seen that certain forms of jaundice are associated with functional changes in hepatic cells. The liver performs a variety of important functions in the body in addition to the secretion of bile, and we wish now to consider how these other functions are disturbed in hepatic diseases, and to what extent these disturbances may be made evident when the patient is subjected to the so-called functional hepatic tests.

Factors of Safety.—In considering such functional tests, it should be remembered that the liver functions, like most functions in the body, are protected by various factors of safety. Many chemical transformations performed by the liver are not restricted to this organ, and when the liver is damaged or removed these transformations may be performed by other tissues in the body. Furthermore, the liver is a large organ, and, even when a considerable portion is excised or thrown out of function, the remainder may be able to carry on the usual work in a normal manner. It is not to be expected, therefore, that localized diseases of the liver, such as tumors, abscesses, or cysts, evident though they be on physical or anatomical examination, will necessarily cause manifest changes in the hepatic functions. Impairments of liver function are rather to be expected when there is a widespread damage of the hepatic cells, such as occurs in certain toxic or infectious conditions, or in diffuse cirrhosis.

Regenerative Power of Liver.—The liver also possesses remarkable regenerative powers, so that recovery may take place even after extensive excision or death of its cells. This also must be considered in studies of hepatic function. In certain diseases such as "catarrhal jaundice," infections, and intoxications, the disturbances of liver function are of a transient character. After the etiological factor disappears the cells recover their normal activities. The exact relationship of functional to anatomical changes is often difficult to estimate, especially when, as in catarrhal jaundice, anatomical studies of the liver are so few.

Dissociation of Hepatic Functions.—Finally, it should be remembered that the different hepatic functions are in all probability more or less dissociated from one another, and that an impairment in one does not necessarily mean an impairment in the others. Such a dissociation of functions certainly occurs in diseases of the kidneys, for retentions of nitrogenous waste bear no definite relation to the albuminuria nor to the retention of water or sodium chlorid. The French school, headed by Widal, holds that in jaundice isolated retentions either of the bile pig-

ments or of the bile salts may occur without retention of the other bile constituents. One need not be surprised, therefore, if certain diseases of the liver cells lead to the impairment of one or more hepatic functions, while other functions are left more or less intact. Variations in the results obtained by different hepatic tests do not necessarily cast discredit upon these tests, but may possibly be due to disturbances in specific hepatic functions.

Urobilin in Hepatic Disease

The pigments normally present in the bile are changed in the intestines, and particularly by bacterial action in the colon, into urobilinogen and related compounds. This group of derivatives will be spoken of collectively as urobilin. The urobilin formed in the intestines is in part excreted in the stools, in part destroyed, and in part resorbed by the portal blood stream and carried back to the liver. Normally, the liver removes this urobilin from the blood to such an extent that urobilin does not appear in the urine in readily demonstrable quantities. The following is a schematic representation of the usual sequence as given by Wilbur and Addis:

Liver		Bile Passages		Intestine
Hemoglobin	——>	Bilirubin	——>	Urobilin

	Intestine		Liver
	> Part Excreted		> Part excreted as such in bile
Urobilin	—> Part Absorbed	(Form?)	——> Bilirubin, Hemoglobin (?)
	> Part Destroyed		> Part enters general circulation and is excreted wholly or in part by kidneys.

Urobilinuria in Excessive Hemolysis.—It is evident from this scheme that in conditions of excessive hemolysis there will be an increased excretion of bile pigments by the liver and an increase in the urobilin formed in the intestines. Much of this excessive urobilin leaves the body in the stools, but since an excessive amount is also absorbed by the portal capillaries an unusual strain is thrown upon the hepatic mechanism which serves to remove this from the blood. Not infrequently, therefore, considerable urobilin escapes into the general circulation and is excreted by the kidneys. Urobilinuria may, therefore, occur in conditions of increased hemolysis. To what extent the liver changes that are so frequent in such conditions plays a part in causing the urobilinuria is uncertain. In any case, it is not uncommon to find urobilin (or urobilinogen) in the urine of patients suffering from diseases that are associated with increased blood destruction, such as pernicious anemia, hemolytic jaundice, malaria, paroxysmal hemoglobinuria, and hemorrhages within the body.

After Removal of Obstruction in Common Bile Duct.—The urobilinuria which often occurs when an obstruction in the common bile duct disappears is of similar origin. The excessive amounts of bile pigment that have accumulated in the body are excreted into the intestines, excessive amounts of urobilin are formed and when resorbed some of this may pass the liver and be excreted by the kidneys.

As a Sign of Disturbed Hepatic Functions.—In other diseases, associated with urobilin in the urine, there is no evident increase in the rate of red cell destruction in the body. In such cases, particularly, a urobilinuria suggests that some damage to the liver has interfered with its normal function of removing urobilin from the portal blood. This failure on the part of the liver has permitted the urobilin normally coming from the intestines to enter the circulation in sufficient amounts to be excreted by the kidneys. There is also evidence that some urobilin may be formed, at least under pathological conditions, in the liver itself or in the bile passages, but, as a rule, urobilinuria is absent or insignificant when there is a complete obstruction of the common bile duct, because bile does not enter the chief site of urobilin formation, i. e., the intestines. In the absence of increased blood destruction, therefore, the presence of urobilin or of urobilinogen in the urine may be taken to indicate some disturbance of hepatic function. Unless bile pigments are reaching the intestines, however, no urobilinuria ordinarily occurs.

Clinically these pigments are often present in considerable quantities in the urines of patients suffering from hepatic cirrhosis. Urobilinuria is evidence of functional changes in the enlarged livers of alcoholic persons. It occurs in acute yellow atrophy, and in phosphorus and chloroform intoxications, all of which damage the hepatic cells. In the chronic passive congestion of cardiac insufficiency urobilinuria is not common, but when present it indicates advanced injury to the hepatic parenchyma. In infectious diseases, such as typhoid, pneumonia, measles, scarlet fever, sepsis, etc., urobilinuria is not uncommon, and probably indicates hepatic changes. In some cases, as in the absorption of pneumonic exudates, it may be due in part to the absorption of destroyed red cells. Finally, in incomplete jaundice where bile enters the intestines, urobilinuria may indicate an associated damage to the hepatic cells.

Carbohydrate Metabolism in Hepatic Disease

In view of the fact that the liver plays such an important part in carbohydrate metabolism, it is somewhat surprising that patients with liver disease rarely show glycosuria. Even after the administration of 100 grams of glucose this does not ordinarily develop (see Alimentary Glycosuria). The processes of absorbing, storing, and burning glucose are carried on efficiently even when the liver is markedly diseased. Prob-

ably other tissues than the liver can perform these functions sufficiently well to prevent a demonstrable disturbance in glucose metabolism.

Alimentary Levulosuria and Galactosuria.—In the utilization of certain sugars other than glucose, the liver appears to be more essential; for when these are given in large quantity, they escape into the urine more frequently in the case of patients with diffuse organic liver disease than in the case of normal individuals. Alimentary levulosuria (*q. v.*) is relatively common in certain liver diseases, particularly hepatic cirrhosis and the infectious and catarrhal forms of jaundice. Alimentary galactosuria (*q. v.*) is also common in such patients. When, in accordance with the recommendations of Bauer, an individual is given 40 grams of galactose in 400 to 500 c.c. of tea on an empty stomach, not more than two grams of this sugar should appear in the urine. In catarrhal jaundice, however, this limit of excretion is almost invariably exceeded, a fact which has already been brought forward as evidence of damage to the hepatic parenchyma in this condition. In hepatic cirrhosis the test is also positive in a considerable proportion of cases. In obstructive jaundice from tumors or gall-stones, on the other hand, the galactose test is not infrequently negative and positive tests seem to indicate that there is an associated cholangitis. In chronic hemolytic anemias, in passive congestion of the liver and in febrile conditions the test is usually negative.

Nitrogenous Metabolism in Hepatic Disease

In certain diseases involving the parenchyma of the liver there are found in the urine unusual quantities of ammonium salts, of amino acids, and of other complex nitrogenous compounds. The exact relation of these to hepatic disease is by no means clear.

Disintegration of Hepatic Cells.—One source of these is disintegration of the hepatic cells themselves. In such conditions as acute yellow atrophy, phosphorus poisoning and chloroform poisoning, the liver is the seat of extensive and widespread cellular destruction. Its proteins are disintegrated, and when such livers are removed and kept aseptically at body temperature, they undergo unusually rapid and marked self-digestion (autolysis). It seems certain, therefore, that in such instances of acute hepatic destruction, there are formed unusual quantities of protein decomposition products from the liver substance itself. These products are in part directly responsible for the unusual amounts of amino acids, such as leucin and tyrosin, and for other substances that appear in the urine during these diseases.

Disturbances in the Formation of Urea.—The second possible source of the abnormal nitrogenous material in the urine is an alteration in the rôle which the liver normally plays in protein catabolism. We have seen (page 224) that proteins are broken down by a series of hydrolytic cleav-

ages into simpler nitrogenous compounds which eventually liberate the various amino acids of which they are composed. Following this the nitrogenous complex is separated from the remainder of the amino acid. In some cases (arginin), urea is formed directly. More commonly, however, ammonia is split off from the amino acids. This ammonia unites with carbon dioxid or other acids in the blood and these ammonium salts are later converted into urea.

Excretion of Ammonia in Hepatic Disease.—That the liver normally plays an important part in this final conversion of ammonium salts into urea is certain. Urea is formed when certain ammonium salts are perfused through an isolated liver, whereas the perfusion of other organs yields little, if any, urea. This does not prove that urea cannot be formed elsewhere in the body from ammonium salts; but it indicates that the transformation occurs with particular ease in the liver. In the acute degenerations of the hepatic parenchyma mentioned above and in cirrhosis of the liver, the ammonium salts of the urine have frequently been found to be increased, either absolutely or in proportion to the total nitrogenous excretion. One is tempted to explain such an increase as the result of some disturbance in the urea-forming function of the liver. Yet such does not seem to be the case. In most, if not in all, cases the excess of ammonia in the urine serves to neutralize abnormal acids in the body, and is, therefore, an evidence of acidosis (see Acidosis), rather than of damage to the urea-forming function of the liver. The ability to form urea from ammonium salts is probably a widespread function of the body cells, or, if limited to the liver, it is one that is not readily disturbed in hepatic disease. So far as we know, therefore, the presence of an excess of ammonia in the urine in hepatic disease in man is indicative of acidosis.

"Alkalosis."—It may be mentioned in this connection that Fischler found evidence of an excess of alkali in the body of Eck fistula dogs when he fed them on meat. He believes that the toxic symptoms which these dogs show when fed meat are due to this "alkalosis."

Increase of Amino Acids in Urine.—We have stated that in acute hepatic degeneration amino acids, and particularly leucin and tyrosin, may appear in the urine in considerable quantity, and we have pointed out that these may be derived, in part at least, from the abnormal disintegration of hepatic proteins. Recent studies by Frey and by Falk and Saxl indicate that the amino acid content of the urine may also be increased, though to a lesser extent, in other liver conditions, and especially in hepatic cirrhosis. Similar changes in the urine have also been observed in pregnancy. It hardly seems probable that in such chronic conditions the increase in the amino acid content of the urine is due solely to a disintegration of the liver cells. Possibly there is here some disturbance of deaminization, so that a portion of the amino acids derived from protein catabolism instead of being broken up are excreted as such.

Falk and Saxl found, furthermore, that when certain amino acids were administered by mouth to patients with cirrhosis, a much larger proportion than usual was excreted in the urine, which is additional evidence that in these patients the process of deaminization is impaired. These authors also found that other more complex nitrogenous substances (peptids?) were increased in the urines of their patients.

Parenchymal Cell Damage and Urinary Changes.—It should be noted that these changes in the urines of patients with hepatic disease occur particularly when the damage to the parenchyma cells is relatively severe. They are often absent in conditions which give rise to urobilinuria or to alimentary levulosuria and galactosuria.

Other Functional Disturbances in Hepatic Disease

1. Fibrinogen

The experiments of Doyon, Nolf and their associates indicated that the liver is a normal site of fibrinogen formation. When in animals the liver is seriously damaged by phosphorus or chloroform poisoning, the fibrinogen content of the blood is markedly reduced, and this may be associated with a tendency to spontaneous hemorrhage from the gums or with severe hemorrhage from small skin pricks or cuts (see Hemorrhagic Disease from Diminished Fibrinogen). Whipple has demonstrated a marked reduction in the fibrinogen content of the blood in a fatal case of hepatic cirrhosis with hemorrhages. To what extent such a reduction occurs in less advanced hepatic disease is not known.

Increased Fibrinogen Content of Blood.—Whipple and his coworkers also found that while a drop in blood fibrinogen followed experimental injury to the liver, there was a subsequent rise in the fibrinogen curve above the normal line during the processes of repair. Increases as well as decreases in the fibrinogen content of the blood may, therefore, be associated with changes in the liver functions, and it has been suggested that the increased amounts of fibrinogen observed in infectious diseases, such as pneumonia and septic processes, may be due to an irritative lesion of the hepatic parenchyma.

2. The Blood Lipase

Whipple has called attention to variations in the amounts of lipase in the blood in hepatic diseases. In experimental injuries with chloroform there is a sharp rise in the amount of blood lipase which subsides after a few days. With his coworkers he has also found an increased amount of lipase in the blood of certain eclampsia patients as well as in patients with various types of liver necroses.

3. The Elimination of Phenoltetrachlorphthalein

Abel and Rowntree showed that this colored compound is eliminated through the liver, and the latter has proposed that it be used as a functional test of hepatic efficiency in much the same way as other dyes have been used to test renal efficiency. For this purpose phenoltetrachlorphthalein is injected intravenously and the quantity eliminated in the stools is measured. In diffuse hepatic diseases the quantity eliminated is reduced.

Cholemia

Patients with acute hepatic degenerations, as well as patients in the terminal stages of hepatic cirrhosis, not infrequently present a clinical picture which suggests a severe intoxication. Particularly prominent in this picture are the nervous symptoms, such as twitchings, ataxia, somnolence, and coma. To this group of toxic symptoms, insofar as they depend upon liver changes, the name cholemia has been given. That these symptoms are not due, as was once supposed, to the action of retained bile constituents now seems definitely established. Although serious toxic effects can be produced experimentally by the injection of bile and particularly of bile salts, it is improbable that the concentration of these in the blood of jaundiced patients is ever sufficiently high to give rise to serious nervous symptoms. Complete obstruction of the common bile duct may persist in man for months without the intervention of serious symptoms, and animals which, like the guinea-pig, die as a result of mechanical obstruction of the common duct show at autopsy extensive necroses of the hepatic parenchyma. These liver changes rather than the jaundice itself appear to be the cause of the fatal result.

In many cases and particularly in severe infectious jaundice, the toxic symptoms are due in large part to the infection.

Toxic Symptoms in Eck Fistula Animals.—In other cases, however, the symptoms seem to depend upon changes in the parenchyma of the liver. The toxemia in such patients is probably due either to poisonous substances derived from the disintegrating liver cells or to some change in the intermediary nitrogenous metabolism. Dogs with a fistula between the vena porta and the inferior vena cava (Eck fistula) frequently die of an intoxication characterized by pronounced nervous symptoms. It was noted by Pawlow, Nencki and their coworkers that the feeding of meat to such animals often induced the toxic symptoms. According to Fischler, two types of intoxication occur in Eck fistula dogs. The first, which is due to degenerative necrotic lesions of the liver, regularly causes death with symptoms of manic excitement ending in convulsions or coma. He attributes these liver lesions to injury of the pancreas which

liberates the pancreatic ferments and thus causes the liver necroses. The second type of intoxication is that produced by feeding meat. This is not necessarily associated with degenerative or necrotic changes in the liver and it is not necessarily fatal. It is characterized clinically by blindness, ataxia, stupor and at times slight muscular twitchings and excitement. The latter type of intoxication is due, according to Fischler, to an abnormal alkalinity of the body, which results from a disturbance of that portion of the liver function which assists in maintaining the normal reaction of the body fluids. Thus far such a condition has not been observed in man, and it seems probable that the severe intoxications observed in certain patients with hepatic diseases are due directly to the changes in the hepatic cells. The exact cause of the symptoms in such patients is still, however, unknown.

Gall-stones

Frequency

The frequency with which gall-stones occur has been variously estimated. According to Miyake's recent statistics, gall-stones are found in about seven per cent of all individuals coming to autopsy in Germany, whereas in Japan they are found in only about three per cent. Women, and particularly those who have borne children, show gall-stones more frequently than men, the ratio between the two being variously estimated from as high as 6 to 1 to as low as 3 to 2. This greater susceptibility of women has been attributed in part to the use of corsets, in part to mechanical or chemical changes associated with pregnancy. Cholelithiasis is a disease of adult life, the onset of symptoms usually occurring between the ages of 20 and 60.

Composition and Structure

The chief constituents of gall-stones are cholesterin, calcium salts of bilirubin, and organic calcium salts. Small amounts of fats, soaps, lecithin, etc., are also found. In the great majority of stones the principal constituent is cholesterin, which usually makes up from 70 to as high as 98 per cent of the dried substance of the stone. In addition to the above constituents, the stone contains an organic protein framework, which becomes evident when the other constituents are dissolved.

Arrangement of Components.—In the center of nearly every gall-stone there is found a brown nucleus containing coagulated colloid material, calcium salts of bilirubin, and relatively small quantities of cholesterin. About this nucleus, the other constituents may be arranged either in concentric layers or in divergent rays that spread out from the center. This radial structure is characteristic of the so-called *pure cholesterin*

stones. The latter are large solitary stones found in gall-bladders which at the time of examination at least are usually free of infection. The so-called *combination stones* show a central radial portion, composed principally of cholesterin, and a peripheral portion made up of concentric layers of calcium-containing material. According to the statistics of Aschoff, pure cholesterin stones occur in about six per cent of all cases, while combination stones occur in about twenty per cent. The commonest gall-stones, which are found in sixty per cent or more of all cases, are the multiple, small to medium-sized stones which show a *concentric laminated structure.* The successive layers contain varying amounts of cholesterin, calcium salts, and bile pigments. On splitting such a stone through its center, the layers are easily distinguished on account of variations in their color and structure. Stones composed mainly of the *calcium salts of bilirubin* are also found, but these are rare.

Single and Multiple Stones.—Gall-stones may be single or multiple. The single stones are usually the large pure cholesterin stones or combination stones, while multiple stones are usually smaller and show the concentric laminated structure just described. At times a single large stone is associated with numerous smaller stones, or there may be several generations of stones. The structure is relatively constant for all individuals of a given generation, indicating that some common cause has given rise to the various layers of all members.

Pathogenesis of Gall-stones

Certain constituents of the bile, such as cholesterin and bilirubin, are almost insoluble in water. These are held in solution in the bile by other constituents, important among which are the bile salts, fatty substances, etc. Bile may be concentrated without precipitating its solids and even the addition of considerable lime water does not necessarily throw down the bilirubin. It is evident, therefore, that a simple increase in the amount of cholesterin, of bile pigments, or of calcium salts in the bile cannot be the sole cause of a precipitation of these substances. Other changes must play a part. Yet an increased concentration of these substances may well be a contributing factor in the pathogenesis of cholelithiasis and for this reason the causes of such increases will first be considered.

Increased Cholesterin Concentration.—The cholesterin of the bile is excreted in part by the hepatic cells, in part it is derived from the mucous membrane lining the gall-bladder and the biliary passages (Naunyn). Recent studies have shown that the concentration of cholesterin in the blood is increased in certain pathological conditions, among which are severe types of diabetes, obstructive jaundice, during the later months of pregnancy, during convalescence from typhoid fever, and in some patients with arteriosclerosis and nephritis. According to McNee, hypercholes-

teremia may lead to an increase in the amount of cholesterin in the bile. The view that such a "cholesterin diathesis" may play a part in the pathogenesis of cholelithiasis is suggested by the frequent association of some of the above conditions (pregnancy, typhoid fever) with gall-stones, as well as by the recent observations of Chauffard's school and of Henes who found that in certain patients with cholelithiasis the amount of cholesterin in the blood is increased. The low incidence of cholesterin stones among the Japanese may also be due to the small amount of cholesterin in the diet of these people.

Increased Concentration of Bile Pigments and of Calcium.—The excretion of bile pigments is increased whenever there is an increased destruction of the red blood corpuscles. Congenital hemolytic jaundice, in which an excessive destruction of red cells occurs, is at times associated with attacks of biliary colic. In a large proportion of the cases which have come to autopsy or operation, pigment stones composed chiefly of the calcium salt of bilirubin have been found. To what extent variations in the calcium content of the bile predispose to the formation of gall-stones is not known.

Factors Influencing the Solvent Properties of Bile.—There is, therefore, reason to believe that an increase in the concentration of the specific stone formers may play a part in the pathogenesis of gall-stones. Yet the principal cause seems to lie in changes in those factors which normally keep the bile constituents in solution.

Infection.—Such changes may be brought about by infection of the bile. Thus Cramer showed that when typhoid or colon bacilli are grown in bile a precipitate is formed containing calcium salts, bile pigments and a few cholesterin crystals.

Typhoid fever is frequently complicated by an infection of the gall-bladder and it is frequently followed by cholelithiasis. Attacks of cholecystitis may accompany or precede the formation of stones. At autopsy or operation the gall-bladders of patients suffering from cholelithiasis are frequently found to be infected, and bacilli have been isolated from the centers of gall-stones. The primary relation of infection to cholelithiasis is also evident in the experimental production of gall-stones in animals by partially obstructing a duct and introducing an organism of low virulence. It is generally admitted that in most gall-stones infection has played an important primary etiological rôle. Particularly is this true of the stones that are made up of concentric layers. The various layers, the striking similarity in structure of all stones in a given generation, and the occurrence of successive generations, may all be explained on the assumption that changes in the degree of infection have caused variations in the material deposited.

Cholelithiasis without Infection.—While it is generally admitted that infection of the gall-bladder is the main cause of multiple concentric

stones, wide differences of opinion exist as to the pathogenesis of those stones, usually solitary, in which the cholesterin is arranged radially. Aschoff and Bacmeister believe that this type of stone develops in the absence of infection, while others hold that it represents a rearrangement or even a replacement of the elements which had previously been deposited in concentric layers. There is reason to believe that precipitates may form in sterile bile. Thus Bacmeister has shown that the presence of cells may cause a precipitation of cholesterin from sterile bile. Furthermore, a sterile thread inserted into the gall-bladder may become encrusted with the calcium salts of bilirubin even though the gall-bladder remains free of infection. While, therefore, the great importance of infection in the pathogenesis of gall-stones cannot be denied, nevertheless this does not appear to be the sole disturbance which may lead to the precipitation of the bile constituents.

Colloidal Reactions.—Just how these various agents act is not certain. Infection may possibly destroy certain elements in the bile which normally hold the cholesterin and the bile pigments in solution. Physicochemical changes in the bile have also been held responsible for the precipitation of its constituents. According to the theory advanced by Lichtwitz, certain colloids of the bile carry a negative charge of electricity, while proteins introduced into the bile react with calcium salts and then develop a positive charge. In consequence of a reaction between these complex molecular substances carrying opposite electrical charges, there results a precipitation of cholesterin, bilirubin calcium, protein and organic calcium salts. Concentric stones are rich in calcium and protein framework while the radial cholesterin stones are relatively poor in both. Since infection of the biliary passages tends to increase the amount and change the character of the proteins in the bile this would favor the formation of the concentric stones with their high calcium content and rich protein framework.

Secondary Infections in Cholelithiasis

We have pointed out that infection plays an important part in the pathogenesis of gall-stones and particularly of multiple stones that show a concentric structure. Calculi in the bile passages also favor secondary infections. The sterility of any hollow viscus or duct is maintained in large part by its free evacuation. Any stasis produces conditions which are favorable for the growth of organisms that may chance to lodge behind the obstruction. It seems certain that bacteria are not infrequently excreted by the liver into the bile and the presence of a calculus in the gall-bladder or bile ducts favors a retention and multiplication of these microorganisms. That such secondary infections may in themselves lead to new gall-stones or to new layers on old stones is generally admitted.

Many of the more serious consequences of cholelithiasis are due to such infections rather than to the mechanical effects of the gall-stones.

Biliary Colic

Typical attacks of biliary colic are characterized by violent pains beneath the right costal margin which radiate to the right back and shoulder blade. The paroxysms usually begin and terminate abruptly but leave behind some soreness in the region of the gall-bladder. Aside from the fact that biliary colic is usually due to an obstruction of the cystic or common duct by stones or by the products of inflammation, little is known concerning its immediate cause. If one may draw an analogy between biliary and renal or intestinal colic, it would seem probable that the pains are due, not so much to a lesion of the mucous membrane, as to an acute distention of the bile passages with tension and spasms of the muscle fibers lining the distended ducts. Chronic obstructions do not necessarily produce colic, for it is well known that malignant obstructions may cause an enlargement of the gall-bladder without pain. The gradual distention in such cases causes no pain.

Diseases of the Pancreas

Diseases of the pancreas may produce a variety of disturbances. We have already considered the relation between pancreatic disease and diabetes mellitus as well as the disturbances of intestinal digestion and absorption which follows exclusion of pancreatic juice from the duodenum. Aside from these there remain for consideration the relation of pancreatic disease to fat necroses, and the physiological aspects of acute hemorrhagic necrosis of this organ.

Fat Necrosis

A careful examination of the immediate neighborhood of the pancreas at autopsy not infrequently discloses a number of small, opaque, white or yellowish-white areas which on microscopic examination are found to be composed mainly of necrotic fat cells. Occasionally such areas are numerous and distributed through the abdominal cavity, though still most numerous in the region of the pancreas; while still more rarely they occur in distant parts of the body. The majority of patients showing *extensive fat necroses* have been found to have some disease of the pancreas. Experimentally, these lesions have been produced by ligation of the pancreatic duct, by injury to the pancreatic parenchyma and by the injection of commercial pancreatin into the peritoneal cavity. The intimate relation between fat necroses and pancreatic disease is, therefore, well established. Only very exceptionally have extensive fat necroses been observed without demonstrable pancreatic lesions.

Chemistry of Fat Necroses.—Microchemical studies of fat necroses indicate that there has been a cleavage of the fat into its constituents, fatty acid and glycerin. The latter being soluble is washed away, while the former combines with calcium and deposits of insoluble calcium soaps are thus formed.

Action of Pancreatic Ferments.—The intimate relationship between fat necroses and natural or experimental disease of the pancreas, as well as the experimental production of these lesions by allowing pancreatic juice or pancreatin to act on fatty tissue, indicates that fat necroses are due, in most instances at least, to the action of pancreatic ferments upon the fatty tissues. Distant necroses in pancreatic disease suggests that the proteolytic and lipolytic pancreatic ferments have entered the blood or lymph streams and have acted at a distance, a conclusion which is strengthened by the observation that in acute hemorrhagic necrosis of the pancreas the amount of lipolytic ferment in the urine may be definitely increased.

Acute Hemorrhagic Necrosis of the Pancreas

This remarkable condition is characterized clinically by pain in the upper abdomen, vomiting and rapid collapse; pathologically, by extensive necrosis of the pancreatic gland associated with local hemorrhages and very numerous fat necroses throughout the abdominal cavity, particularly in the neighborhood of the pancreas.

Experimental Production.—Acute hemorrhagic necrosis of the pancreas has been produced experimentally by a variety of means. Among these are: (1) ligation of the gland in mass with interference to its blood supply; and (2) the injection into the pancreatic duct of various irritating or destructive substances such as gastric juice, hydrochloric acid, formalin, fats and bile. Positive results have also been obtained in some instances by the injection of various bacteria. On the other hand, simple ligation or occlusion of the pancreatic ducts does not ordinarily lead to hemorrhagic necrosis; nor does the injection of preparations of enterokinase, the activator of pancreatic trypsin (page 174), lead to hemorrhagic necrosis even when combined with ligation of the duct. It seems evident from these experiments that acute hemorrhagic pancreatic necrosis results from damage to the pancreatic cells, either by a serious interference with their blood supply, or by the chemical action of certain substances which have been introduced into the ducts of the gland.

Pathogenesis in Man.—These experiments indicate that acute hemorrhagic pancreatitis in man may be due to various causes. Since the injection of fat or gastric juice into the pancreatic duct may produce the disease, it has been suggested that under exceptional circumstances this may enter from the duodenum and so give rise to the disease. It is

doubtful, however, if such substances ever enter the duct in sufficient quantity to cause hemorrhagic necrosis. Ascending infections through the ducts may account for a certain number of the clinical cases, particularly when combined with some other injury to the gland. Opie has pointed out that the entrance of bile into the pancreas is by no means difficult. The main pancreatic duct and the common bile duct usually unite within the ampulla of Vater and have a common exit into the duodenum. If this exit be blocked by a stone that is not large enough to fill the ampulla, bile may readily be forced from the common bile duct into the pancreatic duct. (See Fig. 69.) Opie has described cases of hemorrhagic necrosis in which small gall-stones were lodged at the exit of the combined ducts in such a manner that bile could easily be forced into the pancreas. That this is an important cause of acute pancreatic necrosis cannot be doubted. That it is the sole cause is, however, improbable.

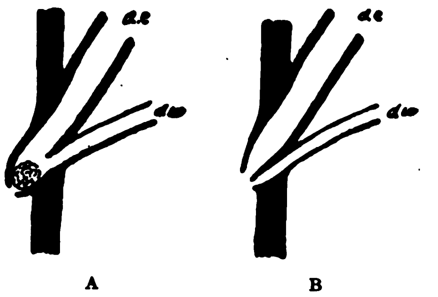

Fig. 69.—Diagram Showing (A) Diverticulum of Vater Containing a Calculus and (B) Separate Entrance of Common Bile Duct (*dc*) and of Duct of Wirsung (*dw*) into the Duodenum. Note that in the Former Bile May Readily be Forced into the Pancreatic Duct. (From Opie, "Diseases of the Pancreas," published by J. B. Lippincott Co.)

Cause of Fatal Symptoms.—The cause of the very severe and often rapidly fatal symptoms that characterize acute hemorrhagic necrosis of the pancreas remains to be considered. These do not depend upon infection, for the experimental disease may pursue a rapidly fatal course in the absence of all infection. The pancreas itself may give rise to highly toxic substances, for the injection of pancreatic tissue into the peritoneal cavities of animals often leads to fatal results. The exact nature of these toxic substances is not known. It seems improbable that they are identical with the pancreatic ferments, for the injection of pancreatic material which has been heated so as to destroy its ferments is also fatal, and examinations of the blood of animals with acute hemorrhagic necrosis have thus far failed to show an increase in the content of trypsin.

Peritoneal Exudate Non-toxic.—The peritoneal exudate which is so common in acute hemorrhagic necroses of the pancreas is non-toxic for other animals, a fact which may be important from the practical standpoint, for drainage of such exudates does not remove toxic material.

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Chapter VII

Disturbances of Respiration

Respiration Proper

Respiration includes all those processes whereby oxygen is delivered to the tissues and carbon dioxid is taken from them and removed from the body. It is evident that these processes fall into two general groups. To the first, the so-called *external respiration,* belong the interchange of gases between the blood and the external air. To the second, the so-called *internal respiration,* belong the transportation of gases in the blood and the interchanges between the blood and the tissues. From the physiological standpoint these two varieties of respiration are intimately associated with each other, for external respiration is controlled mainly by the internal respiration of certain parts of the brain. The two must, therefore, be discussed together.

The Dead Space

Alveolar Ventilation.—Pulmonary ventilation is effected by increasing and diminishing the size of the thoracic cavity. The elastic lungs follow these changes in size and air flows in and out of them through the air passages. During each respiratory movement a certain amount of the air breathed does not reach the alveoli proper, but remains in the trachea, bronchi and other air passages. This air is not available for purposes of respiration, and the space which it occupies is spoken of as the dead space. During shallow breathing the dead space takes up a relatively large proportion of the respired air, while during deep breathing it takes up a relatively small proportion. Edsall has shown that when a normal individual with as little effort as possible breathes first normally, then superficially, and finally deeply, the total external ventilation is greatest in the superficial breathing, and least in the deep breathing. If, however, due allowance be made for the dead space, which must be subtracted from each respiration in order to give the effective ventilation of the pulmonary

alveoli, it is found that the alveolar ventilation is not materially altered by these voluntary modifications of breathing. This may be seen from the following chart:

Breathing	Number of Respirations in 15 Minutes	Total Ventilation in 15 Minutes, Liters	Total Alveolar Ventilation in 15 Minutes Assuming a Dead Space of 140 c.c.
Normal............	174	93.25	68.89
Deep..............	41	71.51	65.63
Superficial.........	465	130.60	65.50

Considered *anatomically,* the dead space is the volume of the respiratory passages through which air must pass before it can be mixed with the alveolar air, and so be brought into contact with the blood in the pulmonary circuit. It is evident, however, that no sharp line of demarcation exists between the air in the alveoli and that in the infundibula and terminal bronchioles, nor is there an abrupt change in structure between the functionating alveolar epithelium and the mucous membrane lining the bronchi. The *functional* dead space is usually estimated by determining what part of the expired air is derived from the alveoli and what part is derived from the air of the previous inspiration. The greater the amount of inspired air that is returned on the succeeding expiration, the greater is the dead space. It is frequently assumed that all the air in the alveoli and infundibula has a constant composition (alveolar air), but such an assumption can hardly be strictly correct and Hoover, for example, believes that changes in the size of the infundibula play an important rôle in certain pathological conditions.

Size of Dead Space.—According to Loewy's calculations, the size of the dead space is usually about 140 c.c. It varies, however, in different individuals, and in a single individual at different times. Siebeck found that in a normal individual the dead space was smaller when the lungs were relatively collapsed, in a position of expiration, and that it was larger when the lungs were expanded, in the inspiratory position. According to Douglas and Haldane, the physiological dead space becomes larger during dyspnea. Thus they estimated that the dead space in a certain individual during rest was 160 c.c. On exercise the dead space increased until, according to their calculations, it reached a maximum of 622 c.c. when the individual was walking at the rate of five miles an hour. These authors assumed that this considerable change was due to a dilatation of the bronchi and bronchioles. On the other hand, Krogh and Lindhard believe that no marked change in the dead space occurs under these conditions.

At the present time we know little concerning pathological variations in the size of the dead space. Siebeck found that the functional dead space is increased in emphysema and in heart disease. According to his determinations the dead space normally varied from 90 to 160 c.c., whereas in emphysema it varied from 190 to 250 c.c. Similar changes appear to occur during cardiac dyspnea. Hoover has also found that the dead space was increased in cases of pulmonary emphysema. An increase in the dead space will necessitate the respiration of larger quantities of air, in order to attain an equal ventilation of the pulmonary alveoli.

Changes in Lung Volume

The total quantity of air which can be made to leave the lungs when a maximum inspiration is followed by a maximum expiration is spoken of as the *vital* capacity. Even at maximum expiration, however, a certain amount of air is left in the lungs. This is spoken of as the *residual air*. This, together with the vital capacity, makes up the *total pulmonary capacity,* the largest amount of air that the lungs can contain. During quiet respiration a certain amount of air is breathed in and out. This is spoken of as the *tidal air,* and the pulmonary capacity at the middle of such a quiet respiration is spoken of as the *midcapacity.* (See Fig. 78.)

Physiological Increases.—All of these quantities vary considerably, both in a single individual at different times and among different individuals. Of particular interest are changes in the midvolume of the lungs. An increase in this midvolume occurs physiologically when an individual passes from the lying to the upright position, when he suffers pain, when he is exposed to cold, when he lives at high altitudes and, as a rule, when he is dyspneic from any cause. The increased volume of the lungs after exercise usually passes off promptly, although after prolonged exertion it may possibly persist for a day or two. The pulmonary volume has also been found to be increased in glass blowers and in those who play musical wind instruments.

Pathological Increases.—Among the pathological conditions which produce pulmonary distention are stenoses of the upper air passages. This has been demonstrated experimentally by breathing through a constricted tube. Distention may occur as a local phenomenon when individual bronchi are narrowed. Acute attacks of asthma cause an enormous pulmonary distention which may disappear in a day or two, or may persist for a much longer time. In emphysema, pulmonary distention is also common and may be very marked. In this condition there is not only an increase in the midcapacity of the lungs, but even more characteristic is the fact that the patient cannot empty his lungs as completely as does the

normal individual. He has an increase in the residual air. Patients with heart disease frequently show some increase in the size of the thorax. Estimates of the amount of air contained in the lungs, however, have shown that as a rule there is no constant or definite increase in the total or midcapacities of the lungs of such patients. According to Plesch, anemia causes an increase in the midcapacity of the lungs.

The Regulation of Pulmonary Ventilation

Afferent Nervous Stimuli

The respiratory movements are controlled by a nervous center lying in the floor of the fourth ventricle. When this portion of the medulla is excised respiration stops. This respiratory center is influenced both by *afferent nervous impulses,* which have traveled mainly over the vagus nerves and by the *composition of the blood* supplied to it. Afferent nervous impulses are not essential for respiration. They serve primarily as a guide to the respiratory movements, in much the same way as the sensory impulses from joints and muscles aid in the control of voluntary movements of the extremities.

Chemical Regulation

Of fundamental importance in the normal regulation of pulmonary ventilation is the hydrogen ion concentration, i. e., the chemical reaction, of the blood which circulates through the respiratory center. Any increase in the acidity of the blood promptly stimulates this center.

Carbon Dioxid Tension.—This conclusion was first suggested by studies of the carbon dioxid tension in the air that fills the pulmonary alveoli. The composition of alveolar air is determined by analyzing samples taken from the last portion of a sharp, forced expiration. By such analyses, Haldane and his coworkers have shown that for each individual the tension of carbon dioxid in the alveolar air is remarkably constant. The normal tension varies in different persons from 39 to 44 mm. Hg., though it may vary from 34 to 48 mm. Hg. (4.5 per cent to 6.4 per cent of an atmosphere). Should the percentage of carbon dioxid in the inspired air be increased, even by a fraction of one per cent, a change takes place in the respirations of the individual. He breathes more deeply and, by so doing, increases his pulmonary ventilation to such an extent that the percentage of carbon dioxid in his alveolar air remains constant.

If, on the other hand, the tension of carbon dioxid in his lungs as well as in his blood is diminished by forced respiration, he becomes apneic and does not breathe again until the tension of carbon dioxid in the blood

has risen to about its normal level. That the apnea following forced respirations is due neither to nervous influences, nor to the increased supply of oxygen, has been demonstrated by showing that it may be prevented, if the normal tension of carbon dioxid in the alveoli be artificially maintained by adding this gas in adequate amounts to the respired air during the forced breathing. Occasionally, as Boothly has shown, there are exceptions to the rule that apnea follows forced ventilation of the lungs. He attributes this to a compensatory diminution of the circulation through the respiratory center.

Hydrogen Ion Concentration.—The action of carbon dioxid upon the respiratory center is not a specific one but is shared by other acids. Respiration is, therefore, controlled in the main by the hydrogen ion concentration (chemical reaction) of the blood that passes through the respiratory center. Any increase in the non-volatile acids of the blood acts as a respiratory stimulant. As a result of this stimulation of the respiratory center by accessory acids, the pulmonary ventilation is increased, the tension of carbon dioxid in the alveolar air is maintained at a relatively low level, and carbon dioxid is pumped out of the blood. In this way the total hydrogen ion concentration of the blood is kept at the normal level. The dyspnea associated with marked reductions in the oxygen content of the blood is believed by Haldane to be due to an abnormal formation of acids in the body, and the same is true of the increased pulmonary ventilation which may persist for some time after muscular exercise.

Changes in the Respiratory Center

Changes in respiration may be due, not only to varying stimulation of the respiratory center by the hydrogen ion concentration of the blood, but also to changes in the irritability of the center itself. To what extent such changes occur under normal or pathological conditions is not definitely known. It seems probable, however, that they do occur. The activity of the center appears to be depressed by morphin (Hasselbalch) and during sleep. Its excitability appears to be increased by caffein (Edsall and Means), by ultraviolet light (Hasselbalch) and possibly by a deficient oxygen supply.

It is apparent that an increased excitability of the respiratory center like an increase of non-volatile acids in the blood will increase the alveolar ventilation and reduce the carbon dioxid tension in the lungs and in the blood. They can be distinguished only by a direct examination of the hydrogen ion concentration of the blood. Such determinations are peculiarly difficult, and since the center is exceedingly sensitive to slight changes, considerable differences of opinion prevail as to the relative rôles played by the center itself and the reaction of the blood coming to it.

The Transportation of Gases in the Blood

Internal respiration depends not only upon the pulmonary ventilation, but also upon the transportation of oxygen and carbon dioxid between the tissues and the lungs. This transportation is governed by two main factors: first, the capacity of the blood for carrying these gases, and, second, the rate of blood flow. It is evident that, other things being equal, the amount of gas that can be carried between the lungs and the tissues varies directly with the amount of blood which passes through the vessels in a given unit of time.

Chemical Compounds.—Both oxygen and carbon dioxid are carried in the blood partly in simple solution but mainly in the form of easily

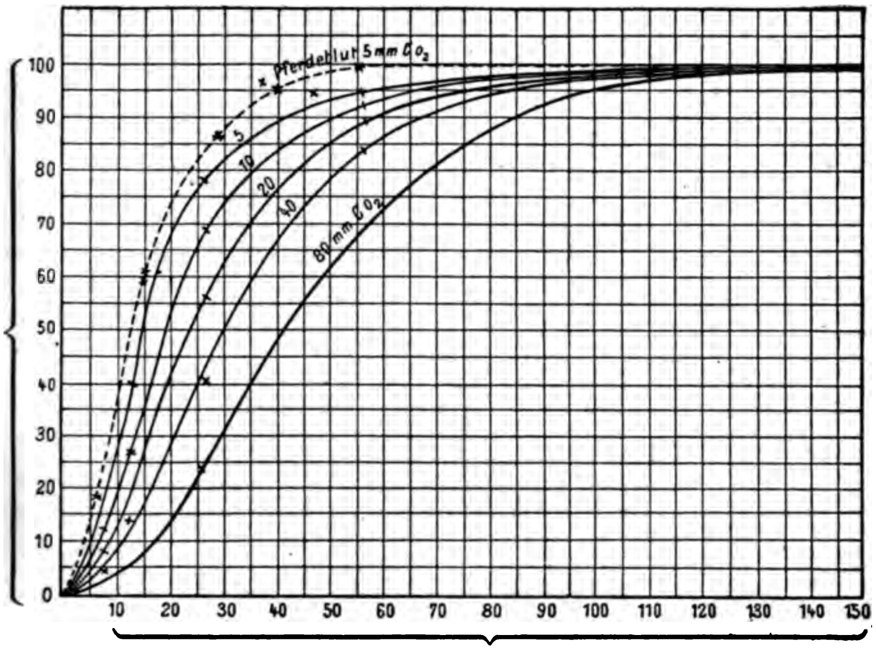

Fig. 70.—Curves Showing the Saturation of Hemoglobin with Oxygen at Different Oxygen and Carbon Dioxid Pressures. The Figures Below Indicate the Oxygen Tension. At Sea Level the Tension in Arterial Blood Is Approximately 100 mm. Note that with Diminishing Tensions the Saturation of Hemoglobin at First Remains Good, But that When the Tension Is Reduced to about 50 mm. with the Usual CO_2 Tension of 40 mm., there Begins an Abrupt Drop in the Saturation of the Hemoglobin. An Increase of Carbon Dioxid in the Tissues Favors the Liberation of Oxygen, As May Be Seen From the Lower Curve. (From A. Loewy, Korányi and Richter's "Physikalische Chemie u. Medizin," published by G. Thieme, Leipzig.)

dissociated chemical compounds. It is well known that the chief oxygen-carrying compound is the hemoglobin of the red blood corpuscles. The amount of oxygen which combines with hemoglobin varies with the tension of the gas, more entering into combination at high than at low pressures.

A definite but complex relationship exists between the tension or partial pressure of oxygen, and the amount taken up by hemoglobin. Ordinary atmospheric air contains about 20 per cent oxygen, and the oxygen tension or partial pressure, therefore, is one-fifth of an atmosphere or 152 mm. of mercury. When blood is exposed to this oxygen tension the hemoglobin becomes nearly saturated with the gas. As may be seen from the accompanying figure, a reduction of the partial pressure of oxygen does not produce a uniform fall in the amount of oxygen that is held in combination by hemoglobin. At first, there is but little change. When, however, with a carbon dioxid pressure of about 40 mm. the partial pressure of oxygen falls to about one-tenth of an atmosphere (76 mm. of mercury), there begins a rather abrupt fall in the oxygen-carrying capacity of the hemoglobin. As may be seen from the figure, this begins earlier and is more marked when large amounts of carbonic (or other) acid are also present. In consequence of these properties of hemoglobin, oxygen is readily taken up by the blood in the lungs, so long as its tension in the alveolar air exceeds about one-tenth of the atmosphere. It is rapidly given off to the tissues when the tension of oxygen in the latter falls much below this point. The distribution to the tissues is facilitated by the presence in them of increased amounts of carbon dioxid, and by any local rise of temperature, for both of these factors increase the dissociation of oxyhemoglobin. In functionating active tissues, therefore, with local heat and carbon dioxid formation, the conditions are peculiarly favorable for disrupting oxygen from the hemoglobin of the blood.

Carbon dioxid is far more soluble in water than is oxygen, but in the blood it is present mostly in loose chemical combinations. In arterial blood, for example, about 2.6 volumes per cent of carbon dioxid are in simple solution out of a total of 40 volumes per cent. The nature of these loose chemical combinations is not well understood. It seems certain, however, that inorganic salts do not contain all of the combined carbonic acid of the blood, and that a considerable proportion is combined with proteins and other organic substances.

Secretion of Gases.—We have assumed that the interchange of gases between the blood and the lungs and between the blood and the tissues always follows the physical laws governing the diffusion of gases. As a matter of fact, most physiological observations accord with this view. Apparent exceptions to the rule have been recorded by Bohr, by Douglas and Haldane, and by others. These authors have therefore assumed that, in exceptional cases and in particular at high altitudes, in carbon monoxid poisoning and during muscular work, the interchange of gases, and especially the absorption of oxygen in the lungs, is assisted by secretory activities of the intervening membranes in the lungs. Krogh and others believe, however, that the interchange of gases in the lungs always follows the physical laws governing the diffusion of gases.

Periodic Breathing

In normal individuals the respirations are, as a rule, fairly regular. Changes in rate or depth occur gradually, and once having occurred the new type of respiration continues or again changes slowly. Under certain circumstances, however, the respirations are irregular. It is well known that the respiratory movements are, to a certain extent, under voluntary control and, consequently, irregular breathing may be due to the influence of the higher brain centers. The deep, gasping breaths occasionally seen in hysterical patients and the changes of respiration caused by emotions and by interest are of this type.

Cheyne-Stokes Respiration.—Of more importance, however, are those irregularities of respiration which are seemingly independent of the higher cerebral centers. The most common of these is known as Cheyne-Stokes respiration. In this condition we have a regular alternation of periods of apnea with those of hyperpnea. This alternation may be of varying degrees. In the milder cases, there is simply a periodic increase and diminution in the size of the respirations. In the more marked cases, periods of complete apnea alternate with periods of extreme dyspnea. Various other manifestations accompany the alternation in respiration. In the severe types, the apnea is associated with drowsiness, the eyes close, and the head drops forward. The pupils may contract, and muscular twitchings may occur. The cyanosis often increases perceptibly. During the period of dyspnea, on the other hand, the patient wakes from his drowsy stupor, the head is thrown back, the pupils are dilated and the respiratory muscles may be strained during the gasping dyspnea. The blood pressure varies during Cheyne-Stokes respiration, but the direction of these variations does not seem to be the same in all patients. In some the blood pressure increases during the dyspnea, while in others it falls.

Periodic breathing of the general type of Cheyne-Stokes respiration is to a certain extent a physiological phenomenon. It is most apt to occur during sleep and it is particularly common in infants. Hypnotics, especially morphin and chloral, favor its occurrence in susceptible individuals. It has been observed in hibernating animals. It is relatively common at high altitudes, particularly those above 9,000 feet. At such elevations the periodic breathing may be so marked when the individual attempts to sleep that it causes serious insomnia. At high altitudes also an unusually deep respiration, or a short period of holding the breath, may initiate prolonged periodic breathing. It will be seen, therefore, that the physiological type of periodic breathing is favored by conditions of unconsciousness, and by diminished atmospheric pressure. In the latter, as we shall see, it is the lack of oxygen which is responsible for the irregular breathing.

Cheyne-Stokes respiration is observed clinically in diseases of the

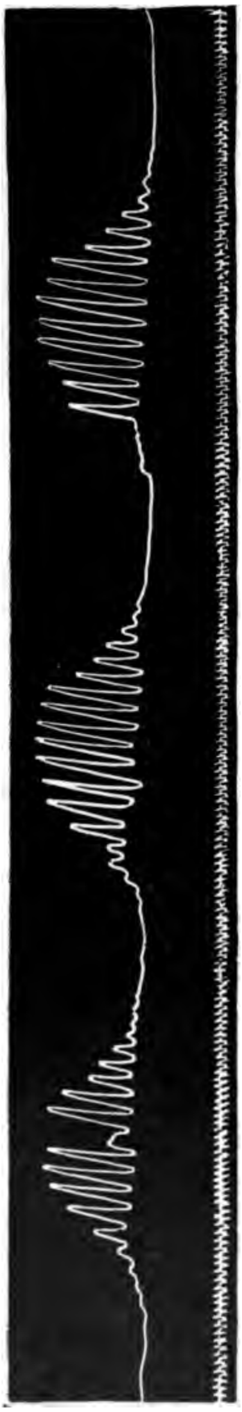

Fig. 71.—Tracing Showing Typical Cheyne-Stokes Respiration. (From Pembrey, Jour. Path. and Bacteriol.)

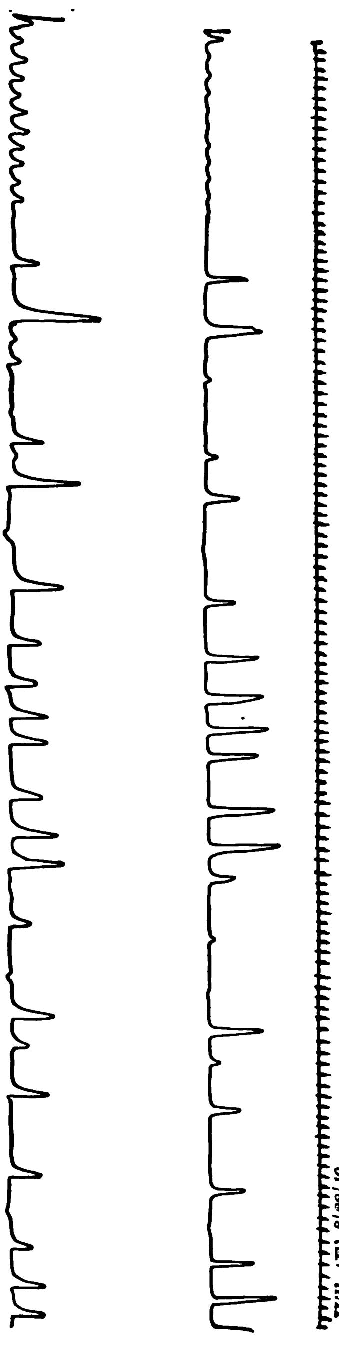

Fig. 72.—Biot's Breathing. Upper Tracing From the Thorax; Lower Tracing From the Abdomen. Downstrokes Indicate Inspiration. (From Conner, Am. Jour. Med. Sci.)

heart, brain and kidney. It is most frequently encountered in cases of arteriosclerosis and chronic hypertension. It also occurs in various diseases of the central nervous system and, among others, in acute increases of intracranial pressure.

Biot's Breathing.—In typical cases of Cheyne-Stokes respiration the periodic changes in breathing occur with a certain regularity. Occasionally, however, irregular breathing does not follow the rhythmic alternation of dyspnea and apnea characteristic of the Cheyne-Stokes type. The irregular respiration known as Biot's breathing, for example, is characterized by great variations in the intervals which separate the respirations, and by irregularity in the size of the individual respirations. This type of breathing occurs particularly in meningitis and is presumably due to a direct involvement of the respiratory center. It should probably be separated from the more rhythmic Cheyne-Stokes type.

Even Character of Normal Respiration.—Many explanations have been offered for the periodic character of Cheyne-Stokes respiration. Before we review these, however, the cause of the regular character of normal respirations may be considered. We have seen that the normal control of respiration depends upon the tension of carbon dioxid in the arterial blood which circulates through the respiratory center in the medulla. One might reason that any sudden increase in this tension would stimulate the respiratory center, increase the pulmonary ventilation, and, as a result, reduce the tension of carbon dioxid in the lungs and in the blood. This, in turn, would lessen the respirations and, through the subsequent accumulation of carbon dioxid in the body, it might be followed by increased respirations. Thus periodic breathing might be established. As a matter of fact, however, sudden changes in the tension of carbon dioxid in the air do not produce periodic breathing. The respiratory mechanism normally acts like an engine with a heavy fly-wheel which prevents sudden fluctuations and oscillations in speed. The explanation for this seems to lie in the fact that the body fluids and tissues have a very large capacity for holding carbon dioxid, and that, on this account, very sudden changes in their content do not occur. The respiratory center is, therefore, affected only gradually by even sudden changes in the alveolar tension of carbon dioxid in the lungs.

While the respiratory center is normally controlled by carbon dioxid tension, it is also extremely sensitive to any marked lack of oxygen. Ordinarily this supply is more than adequate. If it be shut off, however, oxygen want comes on promptly, for, unlike carbon dioxid, there is no great storage of oxygen either in the blood or in the tissues. On account of this small oxygen capacity, it follows that where the oxygen supply is low a further sudden diminution, sufficient to irritate the center, may initiate irregular breathing. This is, indeed, the cause of the forms of Cheyne-Stokes respiration, which will now be considered.

Periodic Respiration from Oxygen Want.—It is well known that prolonged forced breathing is followed by a period of apnea. Not infrequently,

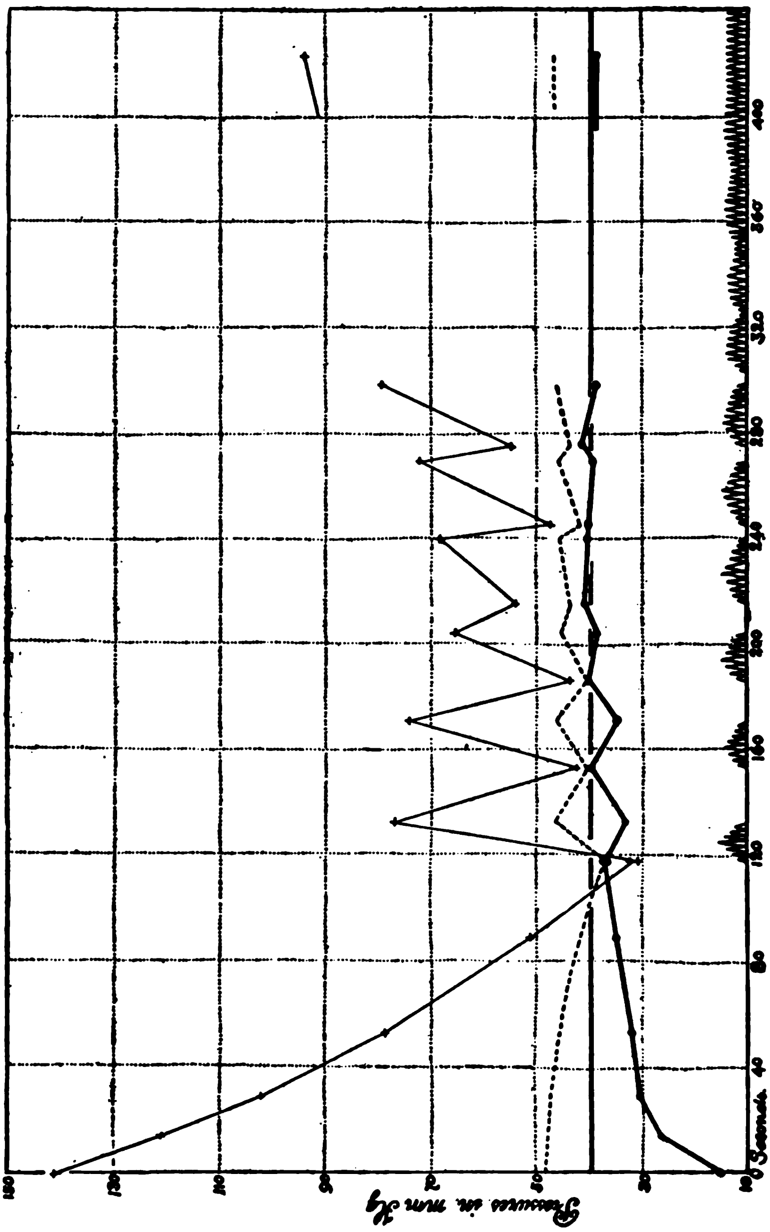

Fig. 73.—The Alveolar Tension of Oxygen (Light Line) and of Carbon Dioxid (Heavy Line) in the Pulmonary Alveoli During the Periodic Breathing that Followed a Series of Forced Respirations. The Irregular Respirations Are Shown at the Bottom of the Figure. Note that the Oxygen Want Played a More Important Rôle than an Excess of Carbon Dioxid, for in Some Cases Respiration Occurred before the Alveolar Tension of CO_2 had Risen to Normal. The Dotted Line Indicates the Irritability of the Respiratory Center, a Fall in this Line Indicating Increased Irritability. (From Douglas and Haldane, Jour. Physiol.)

the respirations which immediately follow this apnea are not regular but are of the Cheyne-Stokes type and this gradually merges into regular breathing. Douglas and Haldane have studied carefully the alveolar gases

during this form of periodic breathing. Their results are charted in Figure 73. This figure begins at the end of the period of forced respiration with a high pressure of oxygen and a low pressure of carbon dioxid in the alveoli. During the first half minute the tension of carbon dioxid rises rapidly, and after this slowly. The oxygen tension, on the other hand, falls rapidly and at a uniform rate until it reaches a level (30 mm. Hg.) at which, as may be seen from Figure 70, the hemoglobin can take up only about one-half the usual amount of oxygen. On account of this lack of oxygen the respiratory center is rendered overresponsive, and is stimulated by a tension of carbon dioxid which has not yet reached the normal stimulating point. Respirations then begin and cause a rise of oxygen tension and a fall of carbon dioxid tension in the alveoli. The respiratory center, being no longer overirritable from lack of oxygen, ceases to act and the patient passes into apnea. These events are repeated several times, but gradually the tension of oxygen rises until finally it keeps the blood sufficiently saturated, and the normal control through carbon dioxid alone is reëstablished. Douglas and Haldane showed that lack of oxygen is essential in this experiment, for periodic breathing does not occur if pure oxygen be inhaled with the last few breaths of the forced breathing, so that the alveolar oxygen tension during the apnea does not fall to a low point. The promptness with which lack of oxygen affects the breathing in this experiment may be explained by assuming that acid products are formed in the respiratory center itself, and that with an increase of oxygen they are rapidly decomposed (Haldane), or by assuming that oxygen want is a direct respiratory stimulant (Gasser and Loewenhart).

Cheyne-Stokes breathing can also be produced artificially by having an individual breathe through a large tube, with a capacity of from 400 to 800 c.c., in which a small vessel containing soda-lime has been placed for the absorption of carbon dioxid. Under these conditions there is no accumulation of carbon dioxid in the lungs, but there is a progressive fall in the alveolar oxygen owing to the unusually large dead space. This lack of oxygen finally affects the respiratory center, and when the individual then overcomes the artificial dead space by deeper respirations, periodic breathing from lack of oxygen occurs. Here, as after prolonged deep breathing, the reduced oxygen supply exerts a periodic effect upon the respiratory center.

It is probable that the type of periodic breathing which occurs at high altitudes is in every way analogous to that produced experimentally by a lack of oxygen. Douglas found that as he ascended to higher altitudes the periodic breathing, which follows the apnea after forced breathing, is more easily produced and lasts for a longer time. At still higher levels it become practically continuous.

Lessened Irritability of Respiratory Center.—We have mentioned that there is a tendency to periodic respiration during sleep, during hiberna-

tion and during the action of hypnotic drugs, such as morphin and chloral. It seems probable that in these conditions there is a lessened irritability of the respiratory center and that in some way this interferes with the normal maintenance of regular respiration. The center, being depressed, does not appear to respond so promptly as it should to slight alterations in the composition of the blood and in this way it permits irregular accumulations of acid products in the blood. Whatever be the explanation of this type of Cheyne-Stokes respiration, it should be noted that during various conditions, which themselves predispose to irregular breathing, such as high altitudes and cardiorenal disease, the irregular breathing is frequently accentuated during sleep. At this time the lessened irritability of the center adds another causative factor to those already present.

Clinical Types.—The most common clinical examples of Cheyne-Stokes respiration are those which occur in association with diseases of the heart, the kidneys and the blood vessels. As yet, few analyses of the alveolar air have been made in these patients. In the case recently reported by White, Ryffel, Poulton, Johnson and Chisholm, the total pulmonary ventilation was increased. The tension of carbon dioxid in the lungs was always low, and examination of the blood showed an increase of non-volatile acids. The alveolar tension of oxygen was, on the whole, high. Even at the end of the period of apnea, there was no marked reduction of oxygen tension below the normal.

ALVEOLAR AIR IN CHEYNE-STOKES RESPIRATION
(FROM WHITE, RYFFEL, POULTON, JOHNSON AND CHISHOLM)

Date	Pulmonary Ventilation Liters per minute (Measured wet at 37° C. and at prevailing atmospheric pressure)	Respirations	Composition of Alveolar Air			
			CO_2		O	
			%	Mm. Hg.	%	Mm. Hg.
April 11th....	15.6	(beginning of dyspnea)	4.2	30	11.7	83
		(end of dyspnea).....	2.3	16	18.4	131
April 16th....	....	....	.....	.....	.....	.....
April 28th....	11.1	(beginning of dyspnea)	4.3	31	15.0	106
		(end of dyspnea)......	3.1	22	18.0	127
May 2nd.....	11.9	....	.....	.....	.....	.....
Normal man.	....	....	5.6	40	14.1 (Approx.)	100
Limits of variations in normal subjects...	10.8	....	5.0	36	.....	.....
	5.6	....	6.0	43	.....	.....

Cardiovascular Changes.—If these observations are confirmed for other patients, then the Cheyne-Stokes breathing of cardiovascular disease cannot be due to insufficient pulmonary ventilation. It is possibly due to circulatory changes, whereby the oxygen supply to the respiratory center is rendered inadequate. The fact that oxygen inhalations frequently relieve Cheyne-Stokes breathing of this type favors the view of a deficient oxygen supply. These circulatory changes may be caused either by a slowing of the general blood stream, or by constriction of the vessels leading to the center. Disturbances in the blood vessels are suggested by the fact that Cheyne-Stokes breathing is frequently associated with general or cerebral arteriosclerosis.

Possibly, as Barbour suggests, the alternations in circulatory velocity depend upon the condition of the heart muscle. During the apnea an

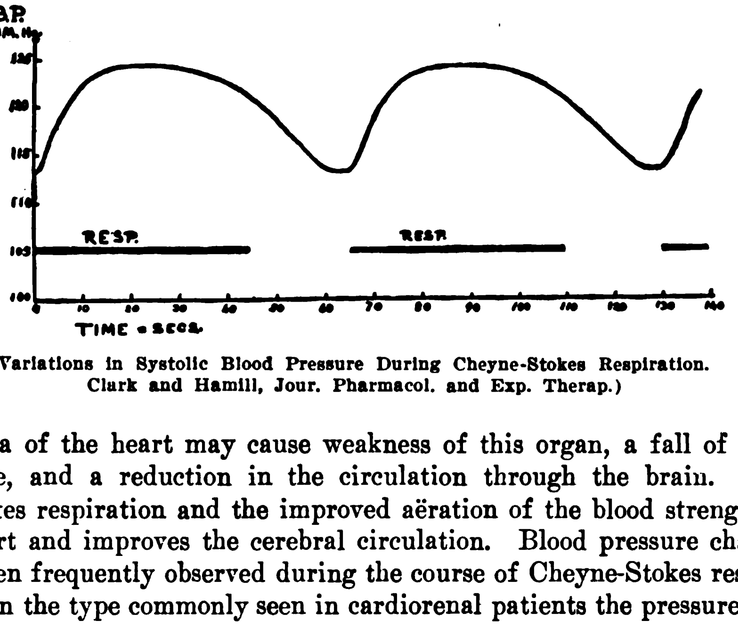

Fig. 74.—Variations in Systolic Blood Pressure During Cheyne-Stokes Respiration. (From Clark and Hamill, Jour. Pharmacol. and Exp. Therap.)

asphyxia of the heart may cause weakness of this organ, a fall of blood pressure, and a reduction in the circulation through the brain. This stimulates respiration and the improved aëration of the blood strengthens the heart and improves the cerebral circulation. Blood pressure changes have been frequently observed during the course of Cheyne-Stokes respiration. In the type commonly seen in cardiorenal patients the pressure falls during the apneic period (Fig. 74).

Cerebral Compression.—We have said that periodic breathing may be produced experimentally by acute cerebral compression. An example of this is seen in Figure 75. This type of periodic breathing occurs when the intracranial pressure has been raised to a high point, approaching or exceeding the normal arterial blood pressure. Under such conditions, the arterial pressure must be elevated above the level of intracranial pressure in order to supply the brain with blood. The pressure rises, yet frequently it does not remain constantly above the level of intracranial pressure, but fluctuates above and below it. When it is above and the brain receives blood the animal breathes; when it is below and the brain is anemic respi-

oxygen to the centers; in other types of Cheyne-Stokes breathing, the dyspnea occurs when the supply of oxygen falls. As Eyster has pointed out, a slight or temporary diminution of the oxygen supply to the center may stimulate it, while a marked deprivation of oxygen over a longer period of time may reduce its irritability. It is doubtful if the type of irregular respiration produced experimentally by high intracranial pressure is comparable to any seen clinically except that due to an acute cerebral compression. The respiratory curves obtained during such experiments are often extremely irregular and resemble those of Biot's breathing. There is also a difference in the relation between the respirations and the blood pressure changes, for while a heightened blood pressure causes the periods of respiration in acute cerebral compression, there is a fall of pressure before the dyspneic periods in the type of Cheyne-Stokes breathing which complicate cardiovascular or renal disease.

Respiration and Acid Intoxication

Carbon Dioxid Tension.—In his experiments on acid intoxication, Walter noted that after rabbits had been given hydrochloric acid the respirations increased, and later workers have shown that the tension of carbon dioxid in the blood of these animals is markedly reduced. The most typical form of acid intoxication in man, that associated with diabetic coma, is also accompanied by large respirations and by a reduced tension of carbon dioxid in the blood and in the alveoli. During the coma itself extraordinarily low tensions may be found (below 10 mm. of mercury in the place of the normal of about 40 mm.). During the less marked acidosis which may precede coma for long periods of time, the alveolar tension is less markedly reduced, ranging from 20 to 32 mm. of mercury. When such patients are given soda by mouth the alveolar tension of carbon dioxid rises, and when soda is taken away it falls. The acidosis which frequently follows sudden carbohydrate starvation in normal individuals (page 292) is also associated with a reduced tension of carbon dioxid in the alveoli and blood.

The reduced tension of carbon dioxid in the alveoli and in the blood during acid intoxications is not due to a reduced capacity of the blood for carrying this gas, but is caused by an increase in the pulmonary ventilation which removes carbon dioxid from the lungs and from the blood more promptly than normal. We have already seen that this increased ventilation is due to the action of acids upon the respiratory center in the brain and that it serves to maintain a normal hydrogen ion concentration in the blood.

Dissociation Curve.—An increase in the concentration of hydrogen ions in the blood also causes a change in the dissociation curve of hemo-

globin. It has been pointed out that this curve is affected by different quantities of carbon dioxid in the blood (Fig. 70), and Barcroft has shown that similar changes in the dissociation curve are produced when lactic acid is added to the blood (Fig. 72).

The presence of abnormal quantities of non-volatile acids in the blood can, therefore, be demonstrated by two methods that have been

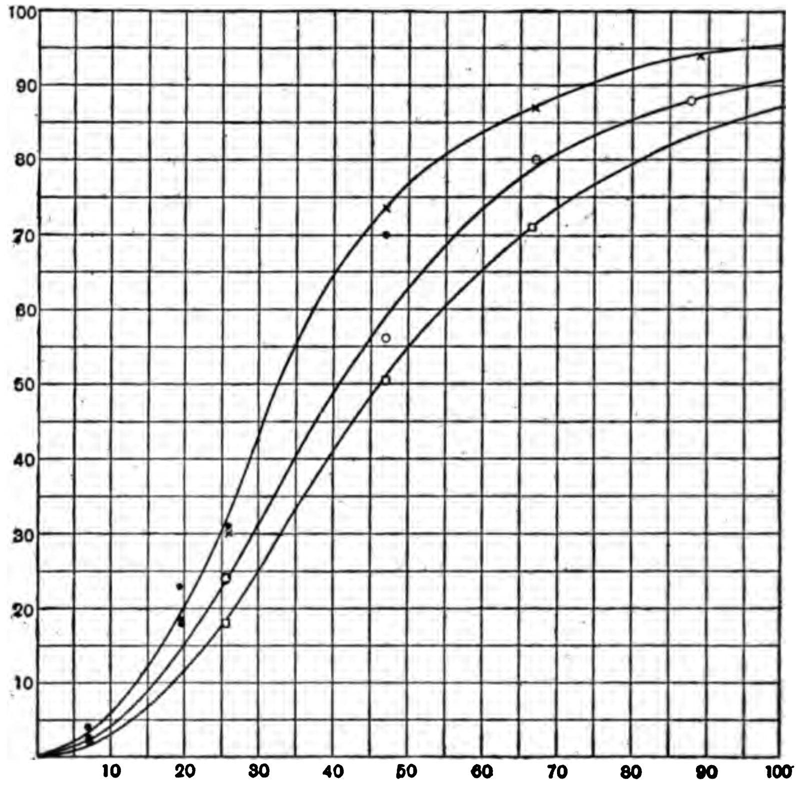

Fig. 76.—Curves of Hemoglobin Dissociation When Lactic Acid Is Added to Sheep's Blood. Percentages of Saturation of Hemoglobin with Oxygen Are Indicated on the Left. The Oxygen Pressure Is Shown Below. The Upper Curve Represents Normal Blood, the Middle Curve Blood Which Contains 0.04 Per Cent Added Lactic Acid, and the Lower Curve Blood Which Contains 0.08 Per Cent Added Lactic Acid. (From Barcroft, Jour. Physiol.)

used in respiratory studies. The first of these is the determination of the tension of carbon dioxid in the alveolar air. When this tension is reduced, it is usually due to the stimulation of the respiratory centers by other acids. The second method is the determination of the dissociation curve of hemoglobin when the tension of carbonic acid is fixed. The presence of abnormal quantities of other acids will then be evident on the dissociation curve.

Respiration at High Altitudes

Mountain Sickness

It is well known that at the great elevations which are attained on high mountains and during balloon ascensions men are subject to a series of disturbances caused by the diminished atmospheric pressure. To these the name of mountain sickness has been given. These symptoms usually begin at heights of 5,000 to 10,000 feet with atmospheric pressures of approximately 630 to 530 mm. of mercury. At very great heights life is impossible. Among the symptoms of mountain sickness are fatigue, prostration, headache, loss of appetite, nausea, palpitation and dyspnea. All these, and especially the dyspnea, are markedly increased on exertion. The breath can be held only a short time. Periodic breathing of the Cheyne-Stokes type is ~~apt~~ likely to occur, and at night this may seriously disturb the sleep. The lips and skin are bluish. These symptoms and signs are most marked during the first two or three days after reaching high elevations. Later they begin to diminish in intensity and, after one or two weeks, a certain amount of acclimatization to the high altitude has taken place.

Lack of Oxygen. — The chief cause of mountain sickness is lack of oxygen. This is shown especially by the immediate relief afforded when pure oxygen is breathed. Here, as in all respiratory conditions, it is the partial pressure of the oxygen rather than the atmospheric pressure which is of the greatest significance. By using oxygen inhalations, balloonists have attained great heights. It is evident, however, that eventually a height will be reached where the pressure of even pure oxygen will be sufficient to maintain life. Loewy places this limit at about 12,000

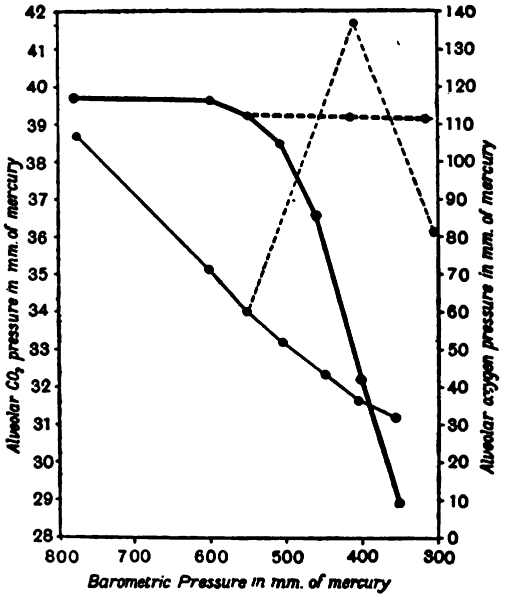

Fig. 77.—The Effect of Reduced Atmospheric Pressures Upon the Tension of Alveolar Gases. Note that As the Tension of Oxygen (Fine Line) Falls, There Is at First No Change in the Tension of Carbon Dioxid (Heavy Line), But that at a Certain Point the Latter Begins to Fall Rapidly on Account of the Increased Pulmonary Ventilation. The Dotted Lines Indicate the Effect of Adding Oxygen to the Air Breathed Without Changing Its Barometric Pressure. (From Boycott and Haldane, Jour. Physiol.)

meters (about 40,000 feet) and states that in order to attain greater heights it would be necessary for the balloonist to live in a closed compartment in which an increased atmospheric pressure could be maintained artificially.

Increased Ventilation.—When a person is exposed to reduced atmospheric or oxygen pressures, certain compensatory mechanisms are brought into play. Boycott and Haldane studied the effect of a few hours' stay in a steel chamber under varying degrees of diminished pressure, and they found that the alveolar tension of carbon dioxid remained constant until a barometric pressure of about 550 mm. of mercury had been reached. Further reductions of pressure caused a rapid fall of the alveolar tension of carbon dioxid, due to an increased pulmonary ventilation. This reduction in carbon dioxid tension at low barometric pressure was caused by the low oxygen tension, for it did not occur if the individual were exposed to equally low barometric pressures when the air in the chamber contained a large percentage of oxygen.

It is well known that, in addition to this mechanism for an immediate increase of the pulmonary ventilation at low oxygen tensions, there are other protective factors which are brought into play during the acclimatization which occurs when individuals live at high altitudes for some time. Under such conditions the increased pulmonary ventilation is greater for a given reduction in oxygen pressure than that which occurs in the acute experiment. According to Zuntz, Loewy, Müller and Caspari, the following increases in pulmonary ventilation occur at different altitudes:

at 1,600 meters about 15 per cent increase
at 2,900 meters about 45 per cent increase
at 3,600 meters about 58 per cent increase
and at 4,560 meters about 114 per cent increase (Loewy).

This increased pulmonary ventilation, which develops gradually, does not immediately disappear on a return to sea level. If, after some weeks' residence at a high altitude, the individual returns to a low altitude, the normal carbon dioxid tension in his alveoli may not be reëstablished for ten days or more.

Cause of Increased Ventilation.—It is evident that in such cases the lack of oxygen is only indirectly responsible for the increased pulmonary ventilation and the reduced tension of alveolar carbon dioxid. Its direct cause is an increased amount of acid in the body, for Barcroft has shown that at high elevations the dissociation curve of hemoglobin corresponds to that seen when small amounts of an organic acid (lactic) have been added to the blood. The acid which is responsible for this change at high altitudes is not known; but the slow return to the normal after a prolonged residence suggests that there has been some fundamental shifting in the relation between bases and acids in the body. Such increases in pulmonary ventilation serve to elevate the partial pressure of oxygen in the alveoli

and in the blood. Naturally, however, they cannot increase the partial pressure in the alveoli beyond the partial pressure of the oxygen in the external air, and their value as a compensatory measure is, therefore, limited by this fact.

Further Protective Factors.—A second compensatory mechanism for aiding the body to withstand the low oxygen pressure of high altitudes is an increase in the hemoglobin and in the number of red corpuscles. This is discussed more fully in another place (page 602), but it may be said, in passing, that this increase in hemoglobin is not due solely to an increase in blood concentration by reason of a reduced volume of blood in the body. After prolonged residence at high altitudes, there is usually either a normal or an increased blood volume. It serves the useful purpose of increasing the oxygen-carrying capacity of the blood. Theoretically the transportation of oxygen to the tissues could also be assisted by a more rapid circulation of blood. At the present time, however, there is no evidence that this plays any important part in assisting respiration at high altitudes.

According to the recent investigations of Douglas, Haldane, Henderson and Snyder on Pike's Peak, a very important method of respiratory compensation at high altitudes consists in an increased secretory activity of the alveolar epithelium. These observers found that, after acclimatization to high altitudes, the oxygen pressure in the arterial blood during rest was about 66 per cent higher than the oxygen pressure in the alveoli, and they attributed this to an active oxygen secretion from the lungs into the blood by the pulmonary epithelium. These results have been criticised by Krogh.

Increased Atmospheric Pressures

Caisson Disease

Pathological disturbances from being subjected to increased atmospheric pressure are rarely encountered except when work must be done below the surface of water or of very yielding earth. Under such conditions the workman, enclosed in a diving suit or working in a so-called caisson, is surrounded by air under sufficiently high pressure to withstand the pressure of the water. Very few physiological effects result directly from such increased barometric pressures. The voice may become hoarse, and sudden changes of pressure on the tympanic membranes may cause disturbances of hearing. The feelings of oppression and of lassitude from which divers sometimes suffer are due, not to the increased pressure but to insufficient ventilation, particularly an excess of carbon dioxid, as well as to an overheating of the body. Animals can withstand enormous increases in atmospheric pressure and only very high pressures are distinctly harmful. Air at 15 atmospheres of pressure or oxygen at 3 atmospheres may

cause convulsions. Of more practical importance, perhaps, is the observation of L. Smith, that pneumonia may result from prolonged exposure to less marked increases of oxygen pressures.

Symptoms from Decompression.—Serious symptoms, therefore, are not produced directly by increased atmospheric pressures. They only develop during or after the release from the high pressure and they are most apt to occur when there has been a rapid decompression. As the French express it, a man pays when he comes out of the caisson. These symptoms of overrapid decompression consist most commonly of severe pains in the extremities, the "bends." In more serious cases, however, stupor, pains and paralyses, referable to the central nervous system, and particularly to the spinal cord, are prominent.

Pathogenesis.—The cause of caisson disease, first definitely established by P. Bert, is the liberation of free nitrogen gas in the blood vessels and in the tissues. In accordance with well-known physical laws, liquids dissolve larger amounts of gas at higher pressures. At one atmosphere of pressure, for example, the blood dissolves approximately one volume per cent of nitrogen, and at two atmospheres it dissolves two volumes per cent. When a person is exposed to an increased barometric pressure, the amount of nitrogen gas dissolved in his blood is increased. The blood rapidly absorbs this extra nitrogen in the lungs and carries it to the various parts of the body. Here the tension of nitrogen also becomes increased. Since, as Vernon has shown, fats dissolve five or six times as much nitrogen as blood, it takes some time (over two hours) before the tissues are saturated with nitrogen. During decompression the reverse changes take place. The extra nitrogen of the blood is given off in the lungs and the reduction in tension allows the blood to take up the extra nitrogen that has been absorbed by the tissues. This is then conveyed to the lungs and eliminated. If sufficient time is not allowed for this transportation and elimination of the nitrogen dissolved in the tissues, a reduction of pressure will set free bubbles of nitrogen gas either within the tissues or within the blood vessels. The latter may act as emboli. The effect which these bubbles produce depends upon their location. The most common of the most serious effects, viz., damage to the spinal cord, is due to a localization of the nitrogen bubbles in this region.

Treatment.—From its pathogenesis it is evident, that caisson disease may be avoided by lengthening the period of decompression, so that there will be an opportunity for the extra nitrogen to escape from the body without forming bubbles within the tissues or blood vessels, and practical experience confirms this view. The occurrence of caisson disease is influenced by various accessory factors. Fat persons are more liable to the disease, probably because their fatty tissues have a greater capacity for storing nitrogen. The time of decompression may be shortened by having the subject exercise, because exercise increases the general rate of circula-

tion very markedly, and so shortens the time for eliminating the nitrogen. Inhalations of oxygen are also of service. By their use the partial pressure of nitrogen in the alveolar air is reduced, and the interchange between the venous blood and the air is more complete. Finally, the symptoms of caisson disease are always improved and often cured if the subject be recompressed as soon as symptoms appear. By this means the bubbles already formed are made smaller, no new gas is liberated, and that already set free is gradually absorbed.

Diminished Oxygen-carrying Capacity of the Blood

When the hemoglobin of the blood is diminished, or when a part of it is converted into compounds which cannot act as oxygen-carriers, the respiration of the tissues is made more difficult on account of the restricted oxygen-carrying capacity of the blood. Normal blood with 100 per cent hemoglobin has an óxygen-carrying capacity of about 18 volumes of oxygen gas per 100 c.c. of blood. Loewy has calculated that with a normal circulation and during rest the blood loses on the average 6.5 volumes per 100 c.c. during its passage through the capillaries. If the hemoglobin in the blood be diminished, the amount of oxygen that can be carried will be proportionately reduced. It is evident, therefore, that, if the hemoglobin were diminished to about one-third of the normal, it would no longer be possible, with the usual rate of circulation, to supply the tissues with the customary amount of oxygen, even though the hemoglobin gave up all of its oxygen. Before this point is reached some compensatory mechanism becomes necessary, if the tissues are to receive their usual supply of this gas.

Carbon Monoxid Poisoning

An acute oxygen deficiency may result from poisoning with carbon monoxid. This gas has an affinity for hemoglobin which is from 150 to 200 times greater than the affinity possessed by oxygen. When blood is exposed to a mixture of these two gases, they are absorbed by the hemoglobin in accordance with this ratio and with the law of mass action, i. e., the relative amounts absorbed are in the proportion of the partial pressure of oxygen to the partial pressure of carbon monoxid multiplied by about 175. For example, exposure to air containing 0.15 per cent of carbon monoxid (equivalent in hemoglobin affinity to 26 per cent oxygen) will cause over half of the hemoglobin to combine with carbon monoxid, and will leave less than half to be combined with oxygen.

Poisoning by carbon monoxid is caused most frequently by exposures to escaped illuminating gases or to the products of incomplete combustion of coal or coke. The poisonous effects result from oxygen-starvation of the tissues, owing to a loss of functionating hemoglobin. Haldane has

shown that carbon monoxid is not toxic except in this way. Animals may be kept alive, even while practically all of the hemoglobin is saturated with carbon monoxid, if they be placed under an oxygen pressure of two atmospheres. At this pressure enough oxygen may be carried in the blood plasma in simple solution to supply the needs of the tissues, and the animal then remains alive.

When a person is exposed to carbon monoxid gas in small quantities it is absorbed gradually by the blood, and symptoms do not usually develop until the latter is about 25 per cent saturated. At this time the patient notices that any unusual exertion causes dyspnea, dizziness and palpitation. With further absorption, throbbing and dizziness become more continuous, and with a saturation between 50 and 60 per cent, mental disturbances begin. Coma develops, and death finally occurs when from 60 to 85 per cent of the hemoglobin of the blood is saturated with carbon monoxid.

In the treatment of carbon monoxid poisoning, the most essential measure is an abundance of fresh air, supplemented by oxygen inhalations. By its mass action the oxygen of the air gradually replaces the carbon monoxid attached to the hemoglobin, and after about three hours the majority of the poisonous gas is eliminated from the body. If pure oxygen gas be administered, the greater partial pressure of the oxygen causes a more rapid disintegration of the carbon monoxid hemoglobin. A larger amount of oxygen is also carried in the plasma in simple solution.

Methemoglobinemia

Hemoglobin may also be rendered inefficient as a carrier of oxygen by being converted into methemoglobin. This conversion is caused by various drugs and infections. Among the former are potassium chlorate, the nitrites, acetanilid, and other coal tar products. The effect of methemoglobinemia upon respiration is similar to the effect produced by carbon monoxid. The patient's appearance, however, is quite different. In carbon monoxid poisoning the skin and mucous membranes have a pink tint, owing to the color of carbon monoxid hemoglobin, whereas in methemoglobinemia the appearance suggests cyanosis on account of the dark color of methemoglobin.

Anemia

A diminished oxygen-carrying capacity of the blood is also caused by anemia. With an acute hemorrhage, the symptoms of oxygen deprivation usually develop when about 50 per cent of the total blood is lost. These symptoms are due in part to the diminished blood volume, and are in part relieved when the loss is replaced by an absorption of fluid from the tissues or the alimentary tract. In the more chronic forms of anemia, patients may live with from 10 to 20 per cent of the normal amount

of hemoglobin to the unit of blood volume. With from 20 to 50 per cent of hemoglobin, they are usually comfortable and may be able to work. Dyspnea appears only on exertion. It is apparent that, in severe chronic anemias, far greater reductions of hemoglobin are tolerated than is the case in carbon monoxid poisoning. Some compensatory mechanism must operate to prevent the dyspnea and other symptoms of lack of oxygen, which we should expect theoretically (page 367) and which we do find in fact in carbon monoxid poisoning.

Respiratory Compensation.—By what mechanism is the anemic patient enabled to accommodate himself to such low percentages of hemoglobin? His total metabolism is not less than normal, and it is often somewhat greater. Only on exertion does the anemic individual show a restriction of his metabolic processes as compared with the normal. The tension of oxygen in his alveolar air is normal, or nearly normal. Indeed, since this tension is normally sufficient to saturate about 96 per cent of the hemoglobin in the blood, little would be gained by increased pulmonary ventilation. The respiratory compensation in chronic anemia must, therefore, lie either in the blood itself, or in the rapidity of its circulation. It was at one time thought that the hemoglobin of anemic blood might differ from that of normal blood in its power to carry oxygen. We now know, however, that this is not the case. The oxygen-carrying capacity of anemic blood is directly proportional to the amount of hemoglobin which it contains.

Two methods remain, which may play parts in making it possible for the anemic patient to carry on his gaseous metabolism in spite of a marked reduction in his hemoglobin. Either the rate of circulation is increased, so that the reduced amounts of hemoglobin are used more frequently for transporting oxygen, or else the oxyhemoglobin which reaches the tissues gives up unusually large amounts of oxygen, and returns to the lungs in an unusually reduced state. It is impossible, at the present time, to determine positively which of these two methods is the more important in the chronic anemias of man. By an indirect method of determining the total blood flow in man, Plesch found that this was always increased in anemias, and that this increase was approximately proportional to the severity of the anemia. According to his view, the anemic patient compensates for his lack of hemoglobin almost entirely by maintaining a more rapid circulation. The hemic murmurs, so frequently encountered in such patients, could then be attributed to the unusually rapid rate of blood flow. It must be admitted, however, that it is uncommon to encounter marked hypertrophy of the heart even after long-continued, severe anemias. We should expect these if, as calculated by Plesch, the heart continually did three or more times its usual amount of work. Wiezacker in experimental anemias did not find any such marked increases in the circulation. Concerning the degree to which the hemoglobin gives up oxygen to the tissues

of anemic patients, there is, likewise, considerable difference of opinion. Plesch found no marked variations from the normal in his gas analyses from the lungs of man. On the other hand, Mohr found a marked reduction in the oxygen content of venous blood taken from animals that had been rendered anemic by hemorrhage. This indicates that the hemoglobin had given up an unusually large proportion of its oxygen during its passage through the tissues. So far as the circulation in the arm of man is concerned, there is usually found in anemia a normal, or even a reduced, blood flow. Consequently, as Morawitz and Röhmer have shown, the anemic blood, in passing through the arm, gives up an unusual proportion of its oxygen. One cannot infer, however, that analogous changes take place in other organs of the body.

Respiration in Cardiac Disease

It is well known that one of the most important symptoms of heart disease is dyspnea. Cardiac dyspnea usually bears a very distinct relationship to exertion. In the milder cases, it may appear only on considerable exertion, while in the more severe cases, it is constantly present but is increased by exercise. The dyspnea of cardiac patients is also frequently affected by posture, and patients often breathe better when they are sitting than when they are lying down. Finally, in some patients with evidences of cardiac insufficiency, and particularly in those who have renal or vascular disease, the dyspnea appears as paroxysmal attacks at night, the so-called cardiac asthma. We shall consider first the commoner type of dyspnea, that which is made worse on exertion.

Cardiac Dyspnea

In a general way, the dyspnea of cardiac patients is more prominent in those types of the disease which are associated with pulmonary congestion. For example, dyspnea is an early manifestation of mitral disease and of insufficiency of the left ventricle, while it is a late manifestation of aortic disease. Conversely, dyspnea is a more serious symptom in aortic than in mitral lesions, for it indicates that the early compensation effected by the left ventricle is beginning to fail.

The degree of cardiac dyspnea bears no constant relationship to the degree of cyanosis. In congenital heart lesions, for example, the cyanosis may be very marked and the dyspnea slight. In patients with arteriosclerosis or renal diseases, on the other hand, dyspnea is often a prominent manifestation of cardiac insufficiency when cyanosis is practically absent. Since cyanosis is caused by an unusually small amount of oxygen in the dilated venules and capillaries at the surface of the body, it is evident

that no definite relationship exists between cardiac dyspnea and a passive congestion of these vessels.

Etiologic Factors.—The causes of cardiac dyspnea are not well understood. Among the possible factors which must be considered are: (1) an insufficient ventilation of the pulmonary alveoli; (2) an insufficient interchange of gases between the blood and the air in the alveoli; (3) a retardation in the flow of blood through the tissues and particularly through the respiratory center, and (4) an acid intoxication. Each of these factors has been held to play a part, more or less important, in the etiology of cardiac dyspnea.

Pulmonary Ventilation.—We have just stated that, from the clinical standpoint, dyspnea is particularly frequent in those cardiac patients who show evidence of pulmonary congestion. In chronic passive congestion of the lungs, the pulmonary capillaries are distended and tortuous, and there is often an exudate of cells and of fluid into the alveolar spaces. There may be, in addition, a complicating bronchitis or bronchopneumonia, particularly in the dependent portions of the lungs. The available lung space within the thorax is frequently reduced by an hypertrophied heart, or by exudates in the pericardial or pleural cavities. Finally, the movements of the diaphragm may be interfered with by an enlarged, tender and congested liver. It is evident, from all these facts, that the dyspnea of many patients with heart disease must depend, in part at least, upon an imperfect pulmonary ventilation.

The effect produced by passive congestion of the pulmonary capillaries upon external respiration has played an important part in past theories of cardiac dyspnea. Von Basch and his school laid great stress upon increased pulmonary volume and decreased pulmonary elasticity, as causes of shortness of breath in cardiac patients. Physical examination of the thorax frequently indicates some enlargement. On the other hand, modern studies have shown that the residual air in cardiac patients is usually normal or only moderately increased, and that the midvolume of the lungs is usually less than the normal. There seems, therefore, to be no increase in the volume of air contained in the lungs. It has been proved, however, that the lungs in cardiac insufficiency are less elastic than normal. Their vital capacity is diminished in nearly all cases, and it may be reduced to 20 or 25 per cent of the normal. From this it is evident that the cardiac patient possesses a smaller reserve than normal in his pulmonary capacity, and that wide fluctuations in the amount of air breathed are not attained as easily as in health. Furthermore, as Siebeck has shown, ventilation of the alveoli in cardiac dyspnea is made more difficult by the fact that an unusually large proportion of the inspired air is breathed out with the next expiration. With respirations of equal size, therefore, the alveolar ventilation in cardiac dyspnea is less perfect than in health. The functional dead space of the lungs (page 348) is increased.

In spite of the unfavorable conditions attending pulmonary ventilation in cardiac disease, this ventilation is as a rule fairly good, owing to the increased respiratory frequency and the normal or increased volume of each respiration. Satisfactory samples of the alveolar air are more diffi-

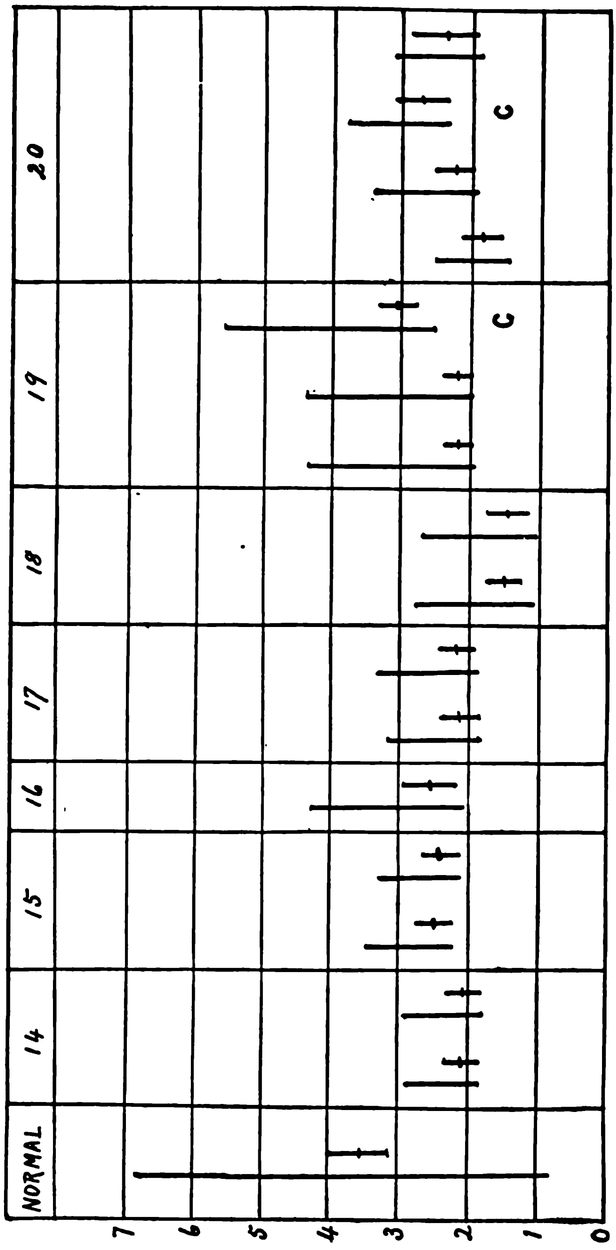

Fig. 78.—Pulmonary Volumes in Cardiac Disease. The Longer Lines Indicate the Vital Capacity and the Distance from the Base Line the Residual Air. The Shorter Lines Indicate the Tidal Air and Their Midpoint the Midcapacity of the Lungs. Note Particularly that in These Patients the Vital Capacity Is Markedly Diminished As Compared with the (Rather Unusually Good) Normal. "C" Indicates Determinations Made During Periods of Compensation. (Redrawn from Siebeck, Deutsch. Arch. f. klin. Med.)

cult to obtain in cardiac patients than in normal individuals, but these have shown in the majority of cases a normal or low tension of carbon dioxid which indicates good ventilation. By Haldane's method of analyzing alveolar air the alveolar pressure of carbon dioxid normally ranges between 35 and 40 mm. of mercury. Of the cases of cardiac and renal dyspnea studied by Lewis, Barcroft, and their associates, the majority showed alveolar tension between 26 and 36 mm., and only two of fourteen patients showed a carbon dioxid tension above the normal.

ALVEOLAR CO_2 TENSION AND ACIDITY OF BLOOD IN CASES OF CARDIAC DYSPNEA

(The latter is calculated from the O saturation of Hemoglobin at 17 mm. pressure in the absence of CO_2.)

(From Heart, 1913, V. 57.)

	Case	Alveolar CO_2	Percentage of Oxygen Saturation	Equivalent of Lactic Acid Necessary to Produce the Same Change in Saturation
Normal	H. H.	39	72	0
	R. G.	36	80	0
	W. S.	40	75	0
Dyspnea with Low Alveolar CO_2	J. P.	26	14	.15
	H. L.	31	44	.05
	D.	29	43	.05
	......	28.5	55	.03
	G. S.	13	14	.15
	F. C.	28	69	.007
	A. S.	27	60	.02
	F. S.	33	48	.04
	......	36	66	.015
	J. S.	..	51	.035
	M. P.	34	61	.02
	H. P.	27	62.5	.017
	C. S.	..	46	.045
Dyspnea with High Alveolar CO_2	T. C.	47	85	0
	E. M.	41	71	0

Porges and his associates obtained similar reductions in patients with cardiac dyspnea. Peabody found no constant change in the alveolar tension of carbon dioxid. It is evident that the unfavorable conditions for pulmonary ventilation present in heart disease are, in most cases, more than compensated by the increased thoracic movements.

Absorption of Oxygen.—Even though pulmonary ventilation were good, there might still be some interference in the interchange of gases between the alveoli of the lungs and the pulmonary capillaries. Analyses of the arterial blood of man are very few. Hürter, who made such analyses in three patients with cardiac decompensation, found that in two the amount of oxygen carried was in each case over 80 per cent of the hemoglobin capacity, while in the third the amount was normal. The dyspnea of

these patients, consequently, could not be attributed to a deficient oxygen saturation of the arterial blood.

So far as we know, therefore, the arterial blood in cases of heart disease is usually saturated with enough oxygen to meet the resting needs of the body, and the carbon dioxid is usually well removed from the blood in the lungs. It follows, therefore, that the respiratory difficulty during rest depends upon an abnormally slow flow of blood through certain or through all of the tissues, which results in an inadequate supply of oxygen to the tissues, or an inadequate removal of carbon dioxid from them.

Acidosis.—Lewis and his coworkers have pointed out that the dyspnea of patients with cardiac insufficiency is frequently associated with an abnormally acid condition of the blood (see table, page 373), and they believe that in the last analysis this acidosis probably depends upon some renal change whereby the normal relation between acids and bases in the body is disturbed. That acidosis tends in general to increase the pulmonary ventilation is well known but to the author it seems improbable that the dyspnea of cardiac insufficiency is due mainly to this cause. This opinion is based on the following considerations: (1) the degree of acidosis is rarely extreme, (2) equally marked degrees of acidosis in diabetes cause an increased pulmonary ventilation (hyperpnea) with no respiratory distress (dyspnea), (3) the administration of sufficient alkalis to cause an alkaline urine does not usually relieve the dyspnea to any material degree, and (4) no definite relation exists between the degree of dyspnea and the degree of acidosis (Peabody). It seems probable, therefore, that while the acidosis is a contributing factor in the production of the dyspnea of cardiac insufficiency, it is not the sole or the chief factor.

Conclusion.—The exact mechanism which leads to the dyspnea of cardiac insufficiency is not known, but the following factors play a rôle in its pathogenesis. In the first place, the acidosis that has been frequently observed in patients with cardiac insufficiency places an unusual burden upon their respiratory mechanisms, for in this as in other forms of acidosis an increased ventilation of the lungs is necessary in order to maintain a normal hydrogen ion concentration of the blood. But the ability of the cardiac patient to meet this excessive requirement is less than the ability of the normal individual. In the first place, his dead space is often increased so that a greater amount of air must be breathed in order to afford an equal alveolar ventilation. In the second place, the vital capacity of such patients may be reduced to one-fourth of the normal. It is evident, therefore, that when unusual requirements develop, as during muscular exercise, the patient with heart disease, already working toward the limits of his respiratory ability, cannot increase his respiratory exchange by the amount that is now necessary, and consequently his dyspnea becomes unusually marked under such a strain.

Cardiac Asthma

The cardiac dyspnea, which we have considered thus far, is induced or is increased by muscular exercise. In addition to this type of dyspnea, patients with heart disease not infrequently suffer from a severe paroxysmal form of difficult breathing. In its most typical form this dyspnea occurs at night and it is then spoken of as cardiac asthma. The patient is awakened with great respiratory distress and he must sit up in order to breathe. Occasionally, such paroxysms are the chief manifestation of the disease; more commonly, they complicate the usual signs of cardiac insufficiency. Not infrequently cardiac asthma is associated with or complicated by attacks of angina pectoris.

Pathogenesis.—The causes of cardiac asthma are varied. The relief afforded by sitting up indicates that the paroxysms are due in part to the recumbent posture. The causes of the more comfortable respirations in the sitting posture will be discussed in the next section.

Nocturnal dyspnea is not infrequently associated with Cheyne-Stokes respiration. We have already pointed out (page 357) that this type of respiration is frequently accentuated during sleep, probably because of a lessened excitability of the respiratory center at this time.

Finally, paroxysms of dyspnea in heart disease may be accompanied by an increased number of râles in the lungs and by the expectoration of blood-tinged sputum. This type of paroxysmal dyspnea occurs particularly in patients who are suffering from chronic myocardial insufficiency, associated with arteriosclerosis, nephritis and high blood pressure. The immediate cause of the attack seems to be an acute congestion of the pulmonary circulation, induced by a relative weakness of the left ventricle. It has been discussed more fully in connection with diseases of the heart (page 95).

Orthopnea

It is well known that patients suffering from dyspnea, and particularly those suffering from cardiac dyspnea, cannot breathe as comfortably when lying down as when sitting up. The dyspnea which necessitates an upright posture is spoken of as orthopnea. The exact cause of orthopnea is not definitely understood. According to the views of earlier authors, the sitting posture allows better *fixation of the shoulders,* and this favors the use of the accessory muscles of inspiration; but Hofbauer showed that these patients experienced their chief difficulty in expiration rather than inspiration. The upright posture is a more favorable one for expiration, because the *anterior abdominal wall is pushed out* by the lower position of the abdominal viscera, and when it contracts during forced expiration it works at a better mechanical advantage. In the sitting posture, also, the

diaphragm takes a lower position. As a result of this, the thoracic cavity is enlarged and the *size of the lungs is increased.* It seems probable that this pulmonary distention assists the pulmonary circulation by increasing the caliber of the pulmonary capillaries. Finally, a high position of the diaphragm may lessen the *aperture traversed by the inferior vena cava,* and it may thus obstruct the return flow of blood from the lower parts of the body. A lower position of the diaphragm, such as occurs in the sitting position, would remove this obstruction. It is difficult, at the present time, to say which of these possible advantages is the most important in contributing to the relief which dyspneic, cardiac patients frequently experience in the sitting posture.

Stenosis of the Upper Air Passages

Stenosis of the upper air passages, though rather infrequent, may be produced by a great variety of causes. Among these are inflammations, edemas and tumors of the larynx, compression of the trachea by tumors, goiters, and aneurisms, the lodgment of foreign bodies in the upper air passages, and spasm of the glottis.

Characteristic Breathing.—In stenosis of the upper air passages the respirations become less frequent but more deep. The respiratory muscles commonly used work more forcefully, and the accessory respiratory muscles are brought into play. Since the inspiratory enlargement of the thorax is not followed by a free entrance of air, there results an unusual negative pressure within the thoracic cavity during inspiration, which leads to retraction of certain portions of the chest wall, particularly the lower lateral portions, the intercostal spaces, and the supraclavicular and the suprasternal fossae. During inspiration the diaphragm may ascend (paradoxical movements). As a rule, inspiration is lengthened more than expiration. The midcapacity of the lungs is increased.

The slow and deep breathing which occurs in stenosis of the upper air passages is distinctly advantageous to the patient, for the same minute volume of respired air gives a greater pulmonary ventilation on account of the dead space factor (page 346).

Pathogenesis.—The cause of the characteristic breathing which develops in stenosis of the upper air passages is not well understood. Morawitz and Siebeck have shown that the dyspnea develops immediately after an artificial stenosis is produced, and before there is time for any change in the composition of the alveolar air. They have shown, furthermore, that in the milder types of stenosis no change in the composition of the alveolar air may be present, and that the total amount of air breathed may even be increased by 50 per cent. It would appear, therefore, that the change in breathing, induced by the milder forms of stenosis of the upper air passages, depends not upon chemical but upon mechanical changes. Ac-

cording to the theory of Hering and Breuer, nervous reflexes play a part in controlling respiration. They believed that each inspiratory distention of the lungs led to expiration through a stimulation of centripetal vagus fibers, and that the expiratory contraction of the lungs in turn caused reflex cessation of expiration, and the subsequent inspiration. The slower respiratory movements during stenosis of the upper air passages can be explained, in part at least, in accordance with this theory, for the above reflexes would not occur so promptly, when expansion or contraction of the lungs was interfered with by an obstruction to the entrance and exit of air. As the stenosis becomes more severe, the ventilation of the alveoli becomes more and more impaired, and there is added the chemical stimulus exerted upon the respiratory center, first, by the increased tension of carbon dioxid and, later, by the lack of oxygen.

Bronchial Asthma

Bronchial asthma is characterized clinically by paroxysms of severe dyspnea, which usually begin at night and usually subside after a few hours, leaving the patient fairly comfortable. In many cases, such attacks recur on successive nights, and there may be more or less shortness of breath between the attacks. The dyspnea of bronchial asthma affects the expiration particularly. This becomes two or three times as long as normal and is associated with activity of the expiratory muscles. The respirations are accompanied by wheezing sounds, and on auscultation numerous small musical râles can be heard over the lungs. These indicate an obstruction to the passage of air through the finer bronchi. Partly because this obstruction is more marked on expiration than on inspiration, the midcapacity of the lungs rapidly increases. In severe attacks there develops an enormous pulmonary distention, with an elevated horizontal position of the ribs, a widening of the inter-

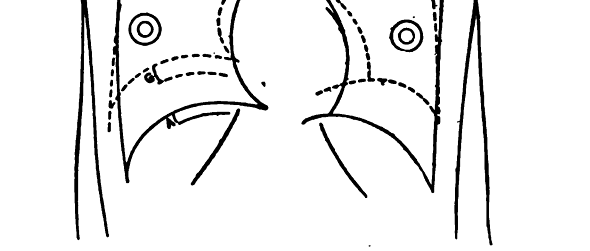

Fig. 79.—Pulmonary Distention During Asthma (Continuous Line) As Compared with Condition Some Weeks Later (Dotted Line). Note the Low Position of the Diaphragm, the Vertical Position of the Heart and the Small Excursion of the Diaphragm (A). (From Warren, Am. Jour. Med. Sci.)

costal spaces, a low position of the diaphragm and a heart that is low, vertical, and in the median line. Ordinarily the pulmonary distention rapidly passes off at the end of the asthmatic attack, but in prolonged and continued attacks, and especially where there has been damage to the pulmonary tissues, restoration to the normal lung volume may take place very slowly. During the attack, the movements of the diaphragm are usually diminished in extent, but otherwise normal. Spasmodic contractions of the diaphragm have been described, but they are not necessarily present and cannot, as some have believed, be the sole cause of the asthmatic paroxysm.

Pathogenesis.—The increased respiratory effort during the attack of asthma is due to a stimulation of the respiratory center. Just how this is stimulated is not known. According to Staehelin and Schütze, the amount of air respired may be greater during the attack than in the intervals. It should be recalled, however, that this does not necessarily indicate a better alveolar ventilation, for, as we have seen, the functional dead space may possibly be increased. Furthermore, the unusual exertion during the attack necessitates a greater interchange of gases. It may be that here, as in high respiratory obstructions, the dyspnea is caused at first by the mechanical effect of the obstruction, rather than by any chemical stimulation of the respiratory center. In severe attacks of asthma, however, a chemical stimulus must be present, for the marked cyanosis so commonly present in such patients indicates a deficient aëration of the blood.

At the present time, all evidence favors the view that during the attack of asthma there is a marked narrowing of the lumina of the smaller bronchi. This narrowing is produced in part by a spasm of the bronchial muscles, and in part by an exudate upon the surface of the mucous membrane. The importance of the exudate is evident from the relief which frequently follows the expectoration of masses of characteristic sputum, containing the spirals of Curschmann, Charcot-Leyden crystals and numerous eosinophilic cells. The sudden onset of the attack and its sudden disappearance suggest that spasm of the bronchial muscles plays an important part. It has been shown that a spasm of the bronchial muscles may be produced in animals by stimulation of the vagus nerve and by certain drugs. The drugs which relieve asthmatic attacks in man most frequently and most promptly, particularly epinephrin and members of the atropin family, also relieve spasms of the bronchial muscles experimentally induced in animals. It seems probable that the spasm of the bronchiole muscles and the exudates on the mucous membranes are both caused by nervous stimuli, which come over the vagus nerve and which stimulate the secreting cells and the muscle fibers.

The etiology of bronchial asthma is but imperfectly understood. A tendency to the disease is often inherited. The attacks themselves fre-

quently appear and disappear in the most capricious manner. A change of residence or of climate may arrest the attacks, and yet one is unable to assign the exact cause of the improvement. As with many other diseases which behave capriciously, much stress has been laid upon the neurotic element in bronchial asthma. We have seen that a spasm of the smooth muscles lining the bronchi may be produced by stimulating the vagus nerve, or by the action of certain drugs, such as pilocarpin, which increase the vagus tone. In certain cases of asthma, the attacks seem to be precipitated and influenced by reflexes arising from the various parts of the body, particularly from the mucous membrane of the nose and nasopharynx. Irritation of these areas may induce an attack of asthma, their cauterization or removal may cure the disease. It may be, as H. Meyer suggests, that asthma depends upon an abnormally irritable condition of the nervous center governing the bronchial muscles. If so, sensory stimuli, which are ordinarily without effect, might cause a paroxysm of asthma in susceptible individuals.

The phenomena attending acute anaphylactic shock in guinea-pigs have thrown new light upon the etiology of bronchial asthma. In these animals acute anaphylaxis is associated with a muscular spasm of the finer bronchi, which closes these air passages. At autopsy the lungs are found distended with air and they do not collapse when the thorax is opened. In certain instances at least, bronchial asthma in man is evidently of a similar character, and is due to an individual sensitiveness toward certain proteins. In the so-called hay-asthma, for example, the attacks are induced in susceptible persons by the inhalation of the pollen of certain plants. In "horse" asthma, the patient develops symptoms when brought in contact with horses. Cases of asthma due to hypersusceptibility to eggs, and to other proteins, have also been described. It is not improbable that all cases of asthma may be due to some special hypersensitiveness to particular protein substances. The association with respiratory infections, for example, may be due to a hypersusceptibility to certain bacterial proteins. At the present time, however, we are unable in most instances to determine to what substance, if any, an asthmatic patient owes his seizure.

Pulmonary Emphysema

Chronic pulmonary emphysema is a disease of the lungs characterized by overdistention of the alveoli with thinning and disappearance of the interalveolar septa. The *senile type* of emphysema which may be regarded as an atrophic process of old age, and the *compensatory form* of emphysema, which occurs about atelectatic lung areas, pleural adhesions, etc., need not be discussed. The usual type of chronic pulmonary emphysema is the so-called *large-lunged variety*. Clinically, this is characterized by the

signs of pulmonary distention and by the frequency with which it is associated with chronic bronchitis, and in the later stages with cardiac weakness. The physical manifestations of pulmonary distention are an increase of the anteroposterior diameter of the chest, a relatively horizontal position of the ribs, an extension of the pulmonary resonance upward, downward and over the heart, and a flattening of the dome of the diaphragm. It should be remembered, however, that not all chronic increases in the size of the chest are associated with the pathological changes usually found in emphysematous lungs, and that they may not be accompanied by the symptoms and sequels commonly associated with this latter disease. For this reason, it is necessary to distinguish an increase in pulmonary volume from an increase which is accompanied by the pathological changes and clinical complications of pulmonary emphysema.

Etiology.—The cause of pulmonary emphysema is still obscure. The view of W. A. Freund, that the distention of the lungs follows a primary enlargement of the bony thorax with fixation in the enlarged position, has not found general acceptance. Freund himself did not find the characteristic bony and cartilaginous changes in all cases of emphysema, and others have expressed the belief that, even when present, they may be secondary to, or coördinate with, the changes in the lungs. Nevertheless, the favorable results which have followed an operative mobilization of the bony thorax in some patients indicates that the bony fixation may play a part in producing the symptoms of emphysema.

The more common view concerning the nature of emphysema is, that it is due to changes in the lung itself, and especially to changes in pulmonary elasticity. The microscopic examination of the elastic fibers in emphysematous lungs has led to varying opinions, some believing that these are reduced or degenerated, others that they show no essential changes. However this may be, the lungs of emphysematous patients do not collapse as completely as the normal when they are taken out of the body, and Bittorf and Forschbach have shown that, when emphysematous patients increase their pulmonary capacity as a result of work or stenosis of the upper air passages, the return to the normal does not occur as promptly as in the healthy individual.

Two Factors.—Two factors, probably, unite to produce pulmonary emphysema. The first of these is a local disease of the lungs which affects the pulmonary elasticity. The second is an unusual distention of the lungs. Thus Hertz reported the case of a cornet player who developed emphysema, when he resumed his occupation after an attack of pneumonia. Subjection of the normal lungs to a distending force, as in a case of glass blowers and the players of musical wind instruments, does not necessarily, nor indeed usually, lead to emphysema. An increase in the midcapacity of the lungs has been demonstrated in glass blowers, without the usual clinical manifestations of pulmonary emphysema.

BRONCHIAL DISEASE.—Pulmonary emphysema is not infrequently associated with chronic bronchitis and chronic asthma. While emphysema predisposes to these conditions, it is also quite certain that the reverse relationship is common. We have seen that an acute attack of asthma may produce an enormous pulmonary distention. Usually, this disappears promptly after the cessation of the attack. It may, however, disappear slowly, and with repeated attacks it tends to persist. Chronic bronchitis favors the development of emphysema in two ways: first, by

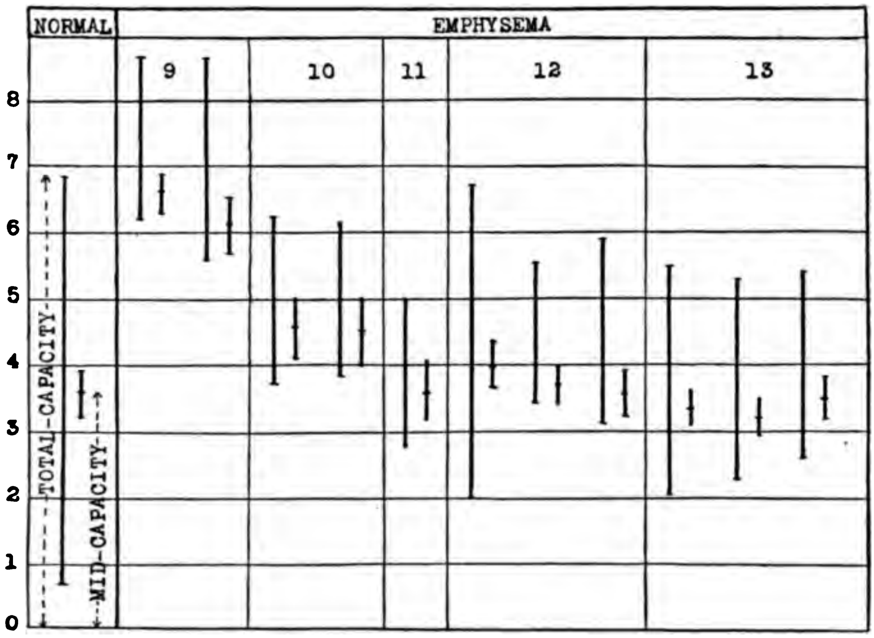

Fig. 80.—The Pulmonary Volume of Emphysematous Patients As Compared with a Normal Individual. Note that the Midcapacity Is Usually, But Not Invariably Increased, and that the Vital Capacity As Indicated by the Longer of the Two Lines Is Diminished. The Most Characteristic Feature of the Change, However, Is the Fact that the Residual Air Is Increased. (Redrawn from Siebeck, Deutsch. Arch. f. klin. Med.)

damaging the pulmonary tissue and presumably lessening its elastic properties, and, second, by obstructing the fine bronchioles. It is well known that a narrowing of the bronchioles allows the air to enter the alveoli more readily than it allows it to escape. This is due in part to the fact that the bronchioles are not rigid tubes. Their lumina vary with the pressure to which they are subjected and, consequently, they are smaller during forced expiration than during forced inspiration.

Residual Air.—The lungs of patients with pulmonary emphysema usually show an increase in the residual air (Fig. 80). Such patients are unable to empty their lungs as completely as the normal. The midcapacity of the lungs is usually but not invariably increased, and the vital capacity

is usually diminished. We have also seen (page 348) that the functional dead space is increased in pulmonary emphysema, i. e., a relatively large proportion of the inspired air fails to remain in the alveoli, but is breathed out of the lungs with the succeeding expiration. As compared to the normal, therefore, the patient with pulmonary emphysema gets a poorer ventilation of his alveoli for the same external respiration. He may make up this deficit by increased respiratory movements, and studies have shown that in emphysema the minute volume of respired air is usually equal to or greater than the normal. Nevertheless, the alveoli may contain unusual amounts of carbon dioxid, and Porges, Leimdörfer and Markovici found an abnormally high tension of carbon dioxid in the venous blood in most cases. The frequent presence of cyanosis also indicates an imperfect aëration of the blood. It is evident, moreover, that the patient with pulmonary emphysema has a smaller factor of respiratory accommodation than the normal individual. The diminution in his vital capacity, and the relatively imperfect mixture of the respired air with that in the alveolar spaces, cause him to suffer from respiratory insufficiency, when work or other causes increase the demand for gaseous interchange.

Respiratory Movements.—The respiratory movements in emphysema are characterized by the prolongation of expiration. Inspiration is usually performed without great difficulty, whereas expiration necessitates the use of the accessory muscles. The diaphragm is relatively flattened and for this reason its descent in inspiration is less marked than in the normal individual. Its contractions draw in the lower thorax, and tend to diminish the costal angle during inspiration, whereas, normally, this angle widens at this phase of respiration.

Secondary Circulatory Changes.—Patients with chronic pulmonary emphysema are peculiarly liable to secondary changes in the circulation. These are discussed elsewhere (page 41). They are due, in part, to the diminished movements of the diaphragm, which normally assist the flow of venous blood from the abdominal organs to the right heart. In part, they are due to a disappearance of the alveolar walls together with their contained capillaries, and to a loss of pulmonary elasticity. The distention of the lungs probably assists the pulmonary blood flow by widening the pulmonary capillaries. In itself, therefore, it tends to compensate to some degree for the other unfavorable circulatory factors.

Loss of Respiratory Surface

In certain diseases some of the respiratory surface in the lungs is thrown out of function, either by the presence of exudates in the alveoli and finer bronchi, or by collapse of the lung from outside pressure. In such cases the exchange of gases between the capillaries and the alveoli is more or less interfered with. The effect of such a loss of respiratory

surface depends largely upon the circulation in the portion of lung, which is thrown out of function. The blood, which passes through this portion of lung, will not be aërated and, when it is mixed with the blood coming from other parts of the lungs, the tension of oxygen in the mixed arterial blood will be proportionately diminished. Loewy has calculated that, with the usual rate of circulation, a passage of one-half of the blood through portions of the lungs where it cannot be aërated will reduce the oxygen content of the mixed arterial blood from about 18 volumes per cent to about 11.5 volumes per cent.

Aëration of Blood.—It should be noted, that this incomplete aëration of the blood comes from the fact that a portion of the pulmonary blood passes through capillaries from which no interchange of gases can take place. Where the loss of respiratory surface is associated with a coincident loss or reduction of the local circulation, then more blood passes through the remaining functioning part of the lungs. Under such circumstances, the effect upon the interchange of gases in the lungs is less serious, for large amounts of blood may be aërated in the pulmonary alveoli. On the other hand, an unusually large blood flow through the non-aërated lung would be highly disadvantageous. The exact extent to which a loss of respiratory surface reduces the circulation through the diseased portion of lung is, therefore, a matter of much importance. Unfortunately, this question has not been finally settled. Sauerbruch held that in pneumothorax more blood flowed through the collapsed than through the normal lung, and believed that the dyspnea resulted from this "short circuiting" of the pulmonary circulation. Other authors, however, have found that the circulation in collapsed or consolidated lungs is poorer than it is through the normal pulmonary tissue. The examination of the oxygen content of arterial blood drawn from the radial artery (Hürter) showed no serious lack of oxygen, in the few cases of chronic pulmonary disease which he examined. In acute pneumonia, the dark color and deficit of oxygen in the blood seems to depend upon the formation of methemoglobin, rather than upon a deficient aëration in the lungs. It seems certain, that only in very extensive lesions of the pulmonary tissue is there a serious lack of oxygen in the arterial blood.

Diseases of the Pleura

Pleural Pain

Among the commoner manifestations of pleural disease is pain. This is characterized by its sharp, stabbing character, and by the fact that it is made worse whenever coughing, deep respirations or other movements cause the opposed pleural surfaces to move on each other. As a result of

this pain and of fear that pain will occur, the respirations in painful pleural affections become short, rapid and superficial.

Capps has shown that in man mechanical irritation of that portion of the pleura which covers the lungs does not cause pain. The parietal pleura, on the other hand, is very sensitive to mechanical irritation, and pain is experienced directly over the spot which is irritated. When the diaphragmatic pleura is touched, the localization of the pain varies according to the portion of the diaphragm irritated. If the outer peripheral portion is irritated, the patient experiences pain over the lower thorax, the lumbar region or the abdomen, localities which correspond to the distribution of the lower six intercostal nerves. When the central portion of the

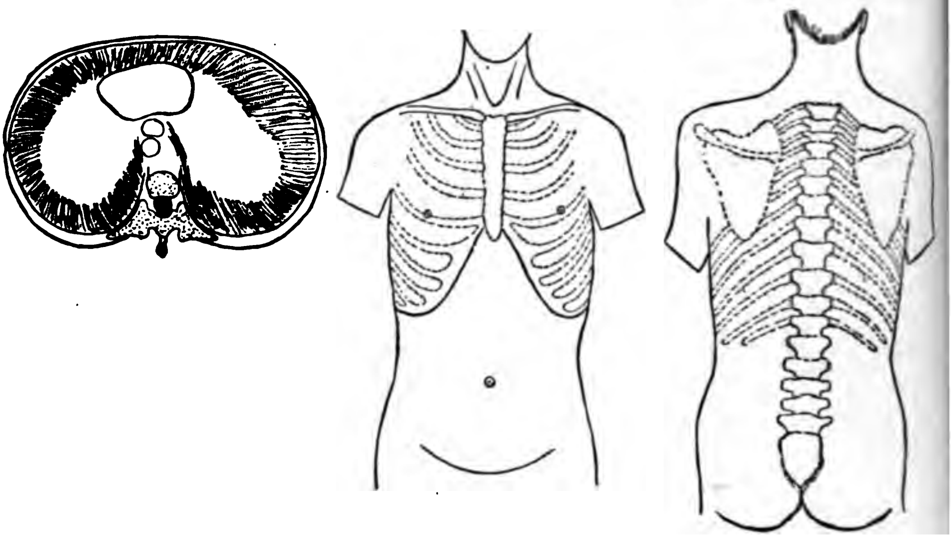

Fig. 81.—Distribution of Pain Elicited on Touching the Diaphragmatic Pleura. Red Dot in the Trapezius Region Indicates the Pain Caused by Touching the Central Tendon of the Diaphragm. Solid Red the Distribution of the Pain Caused by Touching the Peripheral Portion of the Diaphragm. (From Capps, Arch. Int. Med.)

diaphragm is irritated, on the other hand, pain is experienced in the neck above the clavicles, a region which corresponds to the distribution of the nerves coming from the third and fourth cervical segments of the cord. Irritation of the pleura which lines the outer pericardium may also cause pain in this region. We see, therefore, that, while irritation of the pleura lining the thoracic wall causes pain in the immediate neighborhood of the stimulus, irritation of the diaphragmatic pleura causes pain at some distance, either below the thorax or in the neck. Pain is also felt in these regions in diaphragmatic pleurisy. This abdominal pain has at times given rise to a mistaken diagnosis of abdominal disease. Such pains are evidently similar to that which radiates down the left arm in angina pectoris. Their peculiar localization seems to indicate that the pleural surface of the

outer rim of the diaphragm is supplied by the lower six thoracic nerves, while the central portion of the diaphragm receives afferent fibers from the phrenic nerve, which arises from the cervical cord. Irritation of the central diaphragm causes an irritation of the third and fourth segments of the cervical cord, and this causes in turn the pain in the neck observed in disease of the diaphragmatic pleura.

Pleuritic Effusions

When fluid collects in the pleural cavity the lung retracts. Its lower portion, being pressed on by the weight of the fluid, may become collapsed and in time atelectatic. Since the retracted lung tends to preserve its form, the pleural effusion occupies an irregular space bounded on the one side by the inner chest wall, and on the other by the partially or totally collapsed lung.

Intrapleural Pressure.—The pressure within the pleural cavity, when the latter contains an effusion, has been the subject of numerous studies. If fluid be injected into the pleural cavity of a dog in ascending amounts, considerable quantities will be taken without any marked increase in the mean negative pressure, provided this pressure be taken at the upper level of the fluid. The more fluid that is put in, the more the thorax of the animal seems to enlarge, and the positive pressure that is present shortly after a fresh injection soon becomes negative again. Medium-sized dogs will tolerate quantities of liquid in the pleural cavity which approach one liter without any marked rise in the average pleural pressure (Fig. 82). When, finally, the mean pleural pressure becomes definitely positive and continues so, the animal is in a serious condition. It soon becomes cyanotic, the venous pressure rises, and the animal dies if the fluid is not removed. In experimental effusions, therefore, the thoracic cavity seems to increase in size, so as to accommodate the extra liquid, without causing a positive pressure above the level of the fluid.

Direct readings of the pressure in the pleural effusions of man are frequently positive. Gerhardt has shown, however, that, if the pressure obtained be compared with the hydrostatic pressure of the column of liquid within the chest, there is no evidence of a positive intrathoracic pressure at the upper level of the pleuritic effusion. At this point and above there is usually a negative pressure which is equal to, or which may even exceed, the normal negative pressure within the thorax. On the other hand, the lung which dips into the fluid is subjected to a hydrostatic pressure proportional to its depth of immersion. The same is true of the lower mediastinal structures which are displaced toward the opposite side of the chest, and of the diaphragm which is pushed down on the side of the effusion.

The cause of death in massive pleural effusions seems to be an inter-

ference with the circulation. The positive pressure in the lower thorax, which results from the weight of liquid in the chest, compresses the inferior vena cava and interferes with the return of blood from the abdomen. The auricles may also be compressed. Possibly, also, a contributing

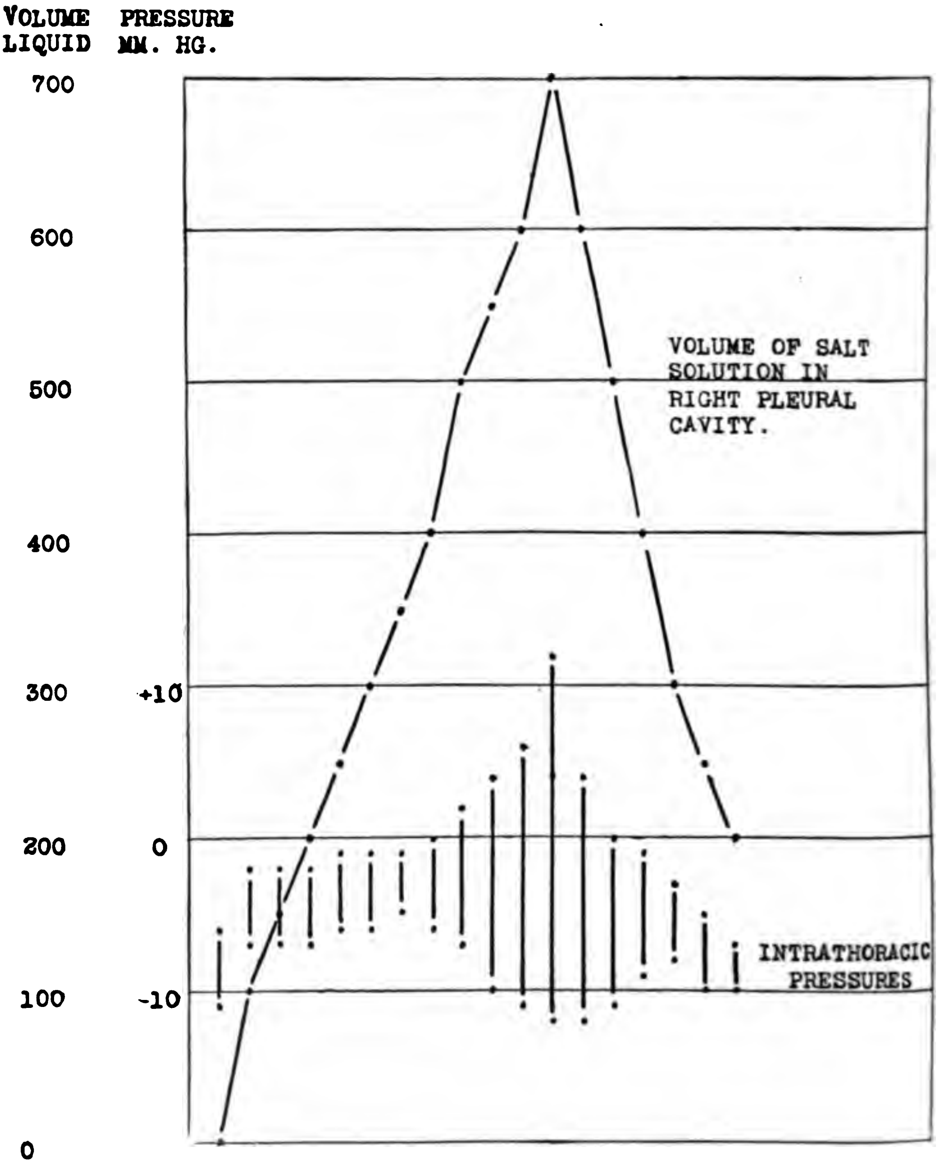

Fig. 82.—Intrapleural Pressures in a Medium-sized Dog When Varying Amounts of Physiological Salt Solution Were Injected Into the Right Pleural Cavity. Note That the Mean Pressure Remains Negative Even Though Dyspnea, As Indicated by the Excursion of Pressure, Is Present. (Constructed from Experiment No. 2, Emerson, J. H. H. Reports.)

factor is an obstruction of the inferior vena cava at the point where it passes through the displaced diaphragm.

Circulatory Collapse.—At times a remarkable type of circulatory collapse occurs during or shortly after the aspiration of fluid from the chest, or in connection with irrigations of the pleural cavity. This collapse is characterized by a slow pulse and a fall of blood pressure. Sometimes it proves fatal. The experimental studies of Capps and Lewis have shown that this circulatory collapse may be produced in animals by irritation of an inflamed visceral pleura. It is due to reflexes which cause, on the one hand, an inhibition of the heart and, on the other, a vasodilation in the abdominal viscera.

Pneumothorax

In pneumothorax there is a collection of gas in one or both pleural cavities. Occasionally, this gas is derived from the decomposition of a pleural exudate. In most instances, however, it is due to an escape of air into the pleural cavity, either from the lungs or through the chest wall, on account of a perforating injury or gross disease of the lung surface. In such cases, there may be a coincident infection of the pleura, which causes an effusion of fluid. More rarely, the pneumothorax is unaccompanied by any exudate. This happens, particularly, in those forms which develop during apparent health, the so-called spontaneous pneumothorax. As a result of the collection of gas in the pleural cavity, the lung on the affected side retracts, the mediastinum moves toward the sound side, the diaphragm on the side affected becomes low, and the bony thorax on this side becomes larger and less mobile.

Open Pneumothorax

The mechanics of pneumothorax vary according to the type of opening which exists between the affected pleural cavity and the external air. In the so-called open pneumothorax there is a free communication between the pleural cavity and the exterior. This is usually due to an extensive opening through the chest wall. It is rare in diseases of the lung, because, in these cases, the opening usually becomes more or less closed as the lung collapses, and free circulation of air between the pleura and the trachea is prevented. In open pneumothorax, the mean pressure within the affected pleural cavity is the atmospheric pressure. The variations which occur during respiration depend largely upon the size of the opening. If this be large, so that air enters and leaves freely, the respiratory variations in pressure are slight. If, on the other hand, the external opening is smaller, then with each respiration more or less marked variations in intrapleural pressure occur, the pressure falling with inspiration and rising with expiration.

When a pneumothorax communicates with the exterior through a wide opening, slight if any respiratory variations in the intrapleural pressure occur on the affected side, and there is, therefore, little or no respiratory movement of the affected lung. The loss of the respiratory function of a single lung is not in itself very serious, provided the respiratory function of the other lung is not interfered with. Unfortunately, in pneumothorax there is always a displacement of mediastinal structures toward the normal side, which tends to reduce the capacity of that side of the chest. More serious than this, however, is the fact that the mediastinal structures thus displaced are movable. In open pneumothorax, they move toward the healthy side with each inspiration and from the healthy side with each expiration. Such mediastinal movements necessarily lessen the respiratory excursions of the healthy lung and seriously interfere with its ventilation. The more lax and movable the mediastinal structures, the more serious will be the respiratory difficulties in an open pneumothorax. If, on the other hand, the mediastinal structures are relatively rigid, either naturally, or from disease, or through mechanical support from the surgeon, the restriction of their movements greatly improves the respiratory mechanics of the healthy lung, and respiration as a whole may no longer be seriously impaired.

Closed Pneumothorax

In the so-called closed pneumothorax no opening exists between the pleural cavity and the exterior. In such a case the intrapleural pressure usually becomes negative, and the mechanical conditions are very similar to those present in pleural effusions. Gases are absorbed from the pleural cavity without great difficulty, oxygen being absorbed more rapidly than nitrogen. An uncomplicated closed pneumothorax usually heals without difficulty.

Valvular Pneumothorax

By far the most important form of pneumothorax from the medical standpoint is that which is known as a valvular pneumothorax. In this type air passes from the lungs, rarely from the exterior, into the pleural cavity with relative ease, but owing to the valvelike action of the collapsed lung, an equally free passage of the pleural air back into the bronchial tree is not possible. In such cases there is a rise of pressure in the affected pleural cavity, and positive pressures of three to ten mm. of mercury have been observed. During inspiration air passes more or less freely from the bronchial tree into the diseased pleural cavity, and at the end of inspiration the enlarged pleural cavity is filled with air at a pressure equal to, or a little less, than the atmospheric pressure. When, on expiration, the pleural cavity becomes smaller, this air cannot escape, and its compression causes the rise in intrapleural pressure. Very deep inspirations tend to

increase the air in the pneumothorax cavity, while forced expirations increase the intrapleural pressure. The dyspnea associated with this type of pneumothorax tends, therefore, to increase both the amount of air in the pleural cavity and the average intrapleural pressure.

In consequence of the positive pressure usually found in valvular pneumothorax the affected lung is compressed and atelectatic, the affected side of the thorax is enlarged, the diaphragm is depressed and the mediastinum is displaced toward the healthy side. The rigidity of the mediastinal structures protects the normal lung from being submitted to the positive pressure present in the pneumothoracic cavity itself.

As a rule, the enlargement of the diseased side of the thorax during inspiration is not followed by any marked expansion of the collapsed lung on this side. During inspiration, therefore, the pressure

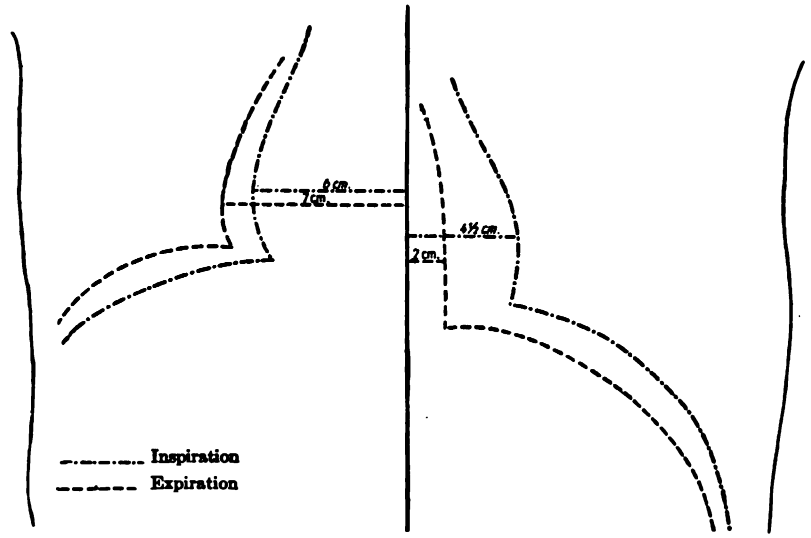

Fig. 83.—Closed Pneumothorax, Showing the Movements of the Mediastinum and Diaphragm During Respiration. Note that During Inspiration the Heart Moves Toward the Diseased Side and that the Diaphragm on this Side Ascends, Whereas on the Normal Side It Descends. The Diminished Heart Shadow During Expiration Is Probably Due to a Rotation of the Heart. (From Wellmann, Deutsch. Arch. f. klin. Med., published by F. C. W. Vogel, Leipzig.)

within the affected pleural cavity tends to fall. The mediastinum is thus drawn toward the affected side during inspiration, and it moves toward the healthy side during expiration. This assists in ventilating the normal lung. The diaphragm on the affected side is low, and its periphery is no longer closely applied to the chest wall. It may execute movements in reverse of the normal, ascending during inspiration and descending during expiration. These paradoxical movements of the diaphragm are due in part to the unusual variations of pressure, which occur during each respiration in a closed pneumothorax, by reason of the lack of expansion

of the atelectatic lung. They are also due to the unusual mediastinal movements. During inspiration, the central portion of the diaphragm moves toward the diseased side and this relaxes this side of the diaphragm and thus permits an elevation of its lateral portion.

Effect on Respiration. — In pneumothorax the respirations are usually increased in frequency, although a normal or slow respiratory rate may also occur. In animal experiments the amount of air respired is usually much below normal if the pneumothorax is an open one, but it may be normal, or above normal, if the opening be closed. In the valvular pneumothorax of man, the amounts of air breathed are usually somewhat less than normal. The cause of the dyspnea in pneumothorax is the change in the aëration of the blood. In experimental pneumothorax of rabbits with a wide external opening, Bruns, as well as Lippert, found that the oxygen content of the arterial blood fell markedly, in some cases to half the normal, while the carbon dioxid content was correspondingly increased. When the pneumothorax was closed, the oxygen content became almost normal, and the carbon dioxid was markedly diminished as compared with the open pneumothorax. At the same time, the deep and strained breathing disappeared.

Analyses of the Arterial Blood in Experimental Pneumothorax

	Normal Breathing Arterial		Open Pneumothorax Arterial		Closed Pneumothorax Arterial	
	O_2	CO_2	O_2	CO_2	O_2	CO_2
1	13.8	46.4	8.4	50.1	13.3	45.0
2	13.75	32.6	11.2	43.2	13.5	33.0
3	15.83	37.2	10.13	57.7	14.8	41.9
4	15.85	41.6	8.74	54.8	15.8	44.8
5	15.65	36.2	8.7	40.7	15.1	39.5
6	16.5	38.9	12.4	40.35	16.4	40.6
7	9.7	51.4	7.5	51.5	9.7	49.1
8	18.9	....	11.9	....	20.1	....
9	....	31.6	....	43.0	....	31.5
10	15.0	47.4	7.3	58.0	14.3	40.3

From this experiment the conclusion is drawn, that in these animals the imperfect aëration of the blood in open pneumothorax is due, not to the short circuiting of a large quantity of blood through the collapsed lung (see page 383), but to an imperfect alveolar ventilation in the sound lung caused by the mediastinal movements. As we have seen, these movements are disadvantageous in open pneumothorax, for the mediastinum moves toward the healthy lung on inspiration and away from it on expiration, thus lessening the amount of air breathed. In closed pneumothorax, on the other hand, the mediastinum makes respiratory movements in the opposite

direction. Experience in surgical operations has also shown, that the respiratory distress following an opening into the pleural cavity is often immediately relieved if the external opening be covered.

Protective Respiratory Mechanisms

The lower respiratory passages are normally free, or nearly free, of microörganisms. In addition to the usual methods of combating entering bacteria, the respiratory passages possess a number of special mechanisms for protecting the lungs against the entrance of microörganisms and of other foreign substances.

Mechanical

Ordinarily, the inspired air first enters the nose. During its course through the irregular passages of the nose and of the nasopharynx, it not only receives warmth and moisture, but many of the small foreign bodies, which it contains, are caught in the mucus, which covers the lining membranes of the respiratory passages. The mucus prevents their immediate penetration into the mucous membranes. It has not been definitely established that this mucus possesses bacteriological properties, though it seems probable that, in some cases of inflammation at least, the cells in the exudate possess such properties.

Cilia

In the bronchi and trachea the mucus, together with any foreign bodies arrested in it, moves more or less continuously in the direction of the mouth, being propelled by the cilia which line this portion of the respiratory passages. Lommel found that the ciliary movements in the trachea of a normal dog were able to transport small particles at the rate of 0.3 to 0.4 mm. per second. It is evident that we have here a valuable means of removing fine particles from the respiratory passage. As the cilia do not extend beyond the epiglottis, expulsion of the mucus beyond that point must be accomplished by coughing. Little is known about pathological changes which may occur in the movements of the cilia lining the respiratory passages. Lommel, who studied these movements in the living dog, found that many measures, which affect ciliary motion in isolated cells, are without effect upon this motion in the living animal. He found, however, that anemia slowed the ciliary movements and that in acute alcoholism they were slowed very markedly. In a marasmic animal with pneumonia the movements had stopped, although microscopic examination showed that cilia were still present.

Smooth Muscle

Beneath the mucous membrane of the air passages is a lining of smooth muscular tissue which is under the control of the vegetative nervous system. It has been suggested that this may assist in the removal of secretions from the lungs by means of peristaltic movements. Such a mechanism would be of particular value in the smaller bronchi. Einthoven observed movements of the bronchial musculature, but there is no direct evidence that these movements are of a peristaltic character. Nevertheless, H. Meyer, on account of the similarity which exists between the bronchial and intestinal muscles in their innervation and pharmacological reactions, regards peristalsis of the bronchial muscles as probable, and it may play an important rôle in the transportation of secretions out of the finer bronchioles.

Coughing

So far as larger bodies in the upper passages are concerned, the most important protective mechanism is coughing. The act of coughing is initiated by a deep inspiration. This is followed by a strong expiratory effort against a closed glottis. After the pressure within the thoracic cavity has been increased, the glottis is suddenly opened, and air from the respiratory passages rushes through at high speed. The nasopharynx is closed off by the soft palate, and any material which is driven out of the air passages enters the cavity of the mouth.

It is evident that, in coughing, the greatest air velocity is attained in the trachea and in the larger air passages. Consequently, it will be most effective in removing sputum or foreign bodies from these regions. When exudates are present in the finer bronchi, or in the alveoli, coughing is much less effective as a method of carrying these toward the mouth. Indeed, if an alveolus is completely filled with exudate, or if a small bronchus is completely blocked, so that air cannot enter during the deep inspiration which precedes the act of coughing, then coughing can have little or no effect in removing the fluid. When, on the other hand, air is permitted to pass into the alveolus during inspiration, then the sudden release of pressure ahead, when the glottis is opened, tends to drive exudates even from the finer bronchi toward the larger air passages.

The act of coughing is controlled by a special nervous center which is situated in the medulla oblongata near the respiratory center. This center is most commonly stimulated by afferent nervous impulses coming from the mucous membrane lining the respiratory passages. Important sites, from which these reflexes may arise, are the region just below the true vocal cords and the bifurcation of the trachea. Reflexes may also arise from the trachea itself and from the bronchi, but they are less sensitive than the points named above. Apparently irritation of the pulmonary

tissue itself does not give rise to coughing reflexes. On the other hand, it is well known that irritation of the pleura may cause coughing. The afferent impulses travel from these sites to the coughing center by way of the vagus nerve. It seems probable, also, that this center may be stimulated by impulses coming from other points of distribution of the vagus, notably from the throat, the esophagus and possibly from the ear, the spleen and the liver. It is doubtful if a true "stomach cough" exists. Occasionally, reflexes from the nose will also produce coughing. In such cases the afferent impulses travel by way of the fifth nerve.

We have already spoken of the value of coughing as a protective measure against the entrance of foreign bodies into the lungs and as a means of removing bronchial mucus. Failure in this protective mechanism greatly increases the danger of pulmonary infections. The aspiration pneumonias which follow operations and deep drunkenness illustrate the dangers of deep narcosis. A disturbance in the reflex arc in organic nervous disease, either on the sensory or on the motor side, is a serious menace to the patient. In certain diseases of the lungs with profuse secretions, coughing may be distinctly impaired, either because of diminished sensation or of great muscular weakness. In prolonged bronchitis, in advanced tuberculosis and in the pneumonia of old and debilitated patients, this constitutes a distinct increase in the danger.

On the other hand, coughing is attended with certain dangers. It puts a strain on certain parts of the pulmonary tissues and tends to distend them. The rise of intrathoracic pressure tends to force air into the unprotected portions of the lungs, especially those lying behind and above the clavicles. In patients with chronic bronchitis and emphysema, the swelling of these portions of the lungs is sometimes plainly visible during coughing. Continued coughing also seems to favor the development of emphysema at the lower and anterior borders of the lungs, partly from the unusual inspiratory effort and partly from the associated closure of the bronchi on expiration. The movements of air toward the apices in coughing tend to carry infections in that direction. Occasionally pneumothorax develops as a result of severe coughing. The blood pressure is raised, and cerebral or other hemorrhages may occur. It is evident, therefore, that excessive coughing has its disadvantages. When it results from causes other than the lodgment of material in the air passages, it serves no useful purpose. This is the case in dry inflammations of the larynx, trachea or larger bronchi, in pleurisy, and in coughs arising from such unusual sites as the nose and the abdominal viscera. It is in such cases, particularly, that the use of drugs for allaying the abnormal irritation of the respiratory center is indicated.

A number of other reflexes are of more or less protective value to the respiratory organs. Among these are reflex spasm of the glottis, which occurs when the upper part of the larynx is irritated, and the reflex cessa-

tion of breathing when irritating gases are breathed. In sneezing we have a mechanism similar to that of coughing, except that the air is discharged mainly through the nose and serves to remove bodies from that organ.

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Chapter VIII

Disturbances of Kidney Function

Physiological Considerations

The kidneys possess a variety of functions. Of these the excretion of urine is the most evident, the most thoroughly studied, and the only one that has thus far been brought into definite relationship with pathological processes. The excretory function serves to remove from the body various waste products of normal or abnormal metabolism. Furthermore, it plays an important part in maintaining a proper concentration of the body fluids and in maintaining the normal chemical reaction of the body.

Unlike that of most glands, the secretory function of the kidney is not, so far as we know, directly governed by nervous impulses. It is true that nervous influences may cause variations in renal secretion but they do this indirectly through changes in the renal circulation. Rises of blood pressure tend in general to increase the amount of urine excreted and falls of blood pressure tend to diminish it. The rate of blood flow through the kidney is also important. If high arterial pressure be associated with a marked constriction of the renal arteries, as in strychnin poisoning, or if the renal veins be obstructed, then the diminished rate of blood flow causes a diminution in the urinary secretion in spite of an increase in local blood pressure. Finally, as Gesell has shown, the secretion of urine is favorably influenced by the intermittent variations in blood pressure which occur with each heart beat.

The renal secretion is also markedly affected by the composition of the blood. When the blood is more hydremic than normal the excretion of water through the kidneys is favored. According to H. Meyer, the behavior of water in the blood plasma may be likened to the behavior of the water present in gelatin. When gelatin contains a considerable amount of water a certain quantity can be readily pressed out, but as the concentration of water falls it is held with more and more avidity. The blood behaves in a similar manner. When an excess of water is present it is readily removed by the kidneys, but when the percentage of water falls to normal or subnormal its excretion is resisted.

The amount of solid material excreted by the kidneys depends in part

upon the composition of the blood and in part upon the volume of urine excreted. When more urine is excreted its concentration is usually low but the total quantity of solid material is for the time being increased. Certain solids, such as urea, are excreted at a rate which seems to depend upon their total concentration in the blood. Other solids, however, notably sodium chlorid and glucose, are not excreted in any considerable quantity unless the blood concentration exceeds a certain threshold. When the concentration falls to about this threshold or below it, the excretion of these solids becomes very slight; when the concentration rises above this threshold the excretion increases rapidly.

The part which the different portions of the kidney play in the excretion of urine, though much discussed, is still quite unsettled. The theories of Ludwig and of Heidenhain, advanced over seventy years ago, still furnish the main basis of physiological discussion. According to the theory of Ludwig, there is a filtration of water containing crystalloids (urea and salts) through the glomeruli. As this filtrate passes on through the urinary tubules, water is absorbed by the cells lining these tubules and in this way a urine of increased concentration is produced. According to the theory of Heidenhain, water is excreted through the glomeruli by a specific cellular activity of the lining membrane, while most of the solid constituents of the urine are secreted by the cells lining the uriniferous tubules. Both theories have been more or less modified with the course of time and both probably contain elements of truth. After a careful review of the subject in 1907, Metzner concluded that it is very probable, as Ludwig claimed, that a filtration of water and salts takes place through the glomeruli and that water, as well as certain solids, is again resorbed by cells lining the urinary tubules. Other substances, however, and especially uric acid, phosphoric acid and foreign substances, are excreted into the urinary tubules by the epithelial cells of the tubules.

It is well known that the molecular concentration of the urine, as measured by the depression of its freezing point below that of water, is ordinarily far greater than the molecular concentration of blood. The freezing point of blood serum is approximately — 0.56°C., while the freezing point of urine usually varies from — 0.87° to — 2.7° C. In order to excrete urine of increased molecular concentration considerable work is required of the kidney; and Dreser has calculated that the excretion of 200 c.c. of a urine with a freezing point of — 2.3° C. requires about 37 kilogrammeters of work.

Polyuria—Diabetes insipidus

From the physiological standpoint an increased amount of urine, or polyuria, may be due (1) to an increased circulation of blood through the kidneys, (2) to a watery composition of the blood, or (3) to an increase

in the secretory activity of the kidney. The latter may result either from increased elimination through the glomeruli or from an interference with the resorption of fluid, which, according to Ludwig's hypothesis, normally takes place in the renal tubules, a veritable renal diarrhea.

Polyuria from Drinking Liquids.—It is a common observation that the amount of urine may be increased by drinking large quantities of liquid. So long as a normal water balance is maintained, the ingestion of more fluid is followed by a corresponding increase in the elimination. If there is no change in the water losses through perspiration, evaporation from the lungs or intestinal discharges, the extra amount taken must be eliminated by the kidneys. In the normal individual this takes place promptly. After drinking a large quantity of water, most of the excess is passed in the urine within a few hours. At the onset of such a diuresis the absolute amount of solids eliminated in a given time is increased. This increase is due to a transient washing out of nitrogenous and other materials from the body by the abundant renal secretion. If the diuresis is continued the total elimination of solids will return to the normal level. Strangely enough, the drinking of even large quantities of water causes no constant and definite reduction in the concentration of the blood plasma, whether this be determined by the refractive index of the serum (concentration of proteins) or by the reduction in freezing point (molecular concentration). The kidneys seem to be sensitive to blood changes which are not demonstrable by these methods.

Polyuria During the Removal of Edemas.—Polyuria also occurs during the disappearance of exudates and edemas. The polyuria in such conditions differs from that which follows the drinking of large quantities of water in that the urine, though usually of low specific gravity, contains greater quantities of sodium chlorid and of urea, which are derived from the absorbed exudates and edematous fluids. In typical renal edema the blood is usually hydremic. It contains a normal or an increased percentage of sodium chlorid but less than the normal percentage of proteins. If diuresis sets in and the edema disappears the blood tends to return to the normal concentration.

Polyurias After Fevers.—During fever there is frequently a diminution in the concentration of the blood and during convalescence there may be an increased secretion of urine with a return to the normal blood concentration. The polyuria in such cases, therefore, resembles in some respects that which accompanies the disappearance of a nephritic edema.

Polyuria from Drugs.—Polyuria may also be produced by various salts and drugs. This is most marked when there is water at the disposal of the kidneys either from ingestion or in the form of absorbable exudates. Changes in the blood, the renal circulation, or the activity of the renal cells may accompany such diureses. After large doses of sodium chlorid, for example, there is a dilution of the blood produced by the abstraction

of water from the tissues. The kidneys enlarge and with this there is usually an increased flow of urine. In some cases the hydremia and kidney changes seem to disappear before the diuresis ceases. Considerable variation exists in the reaction of different individuals to the taking of sodium chlorid. Not infrequently the chief elimination does not occur immediately but may be delayed for a day or more. Under pathological conditions, and especially in certain forms of nephritis, the administration of sodium chlorid not only may fail to act as a diuretic but may diminish both the quantity of the urine and amount of chlorids contained therein. Drugs belonging to the caffein group produce diuresis partly through a direct stimulation of the renal cells and partly through an improved circulation through the kidneys. Digitalis, in addition to its action upon the heart, seems to exert a specific dilating effect upon the renal vessels.

Polyuria in Renal Disease.—Polyuria is not uncommon in renal diseases, especially chronic interstitial nephritis. It also occurs in certain experimental forms of nephritis and is then, according to Schlayer, associated with an excessive irritability of the renal vessels.

Polyuria from Lesions in the Medulla oblongata.—Polyuria may also be produced by lesions of the central nervous system. Claude Bernard showed that injuries to the floor of the fourth ventricle above the diabetic center may be followed by polyuria without glucosuria. This polyuria which is ordinarily of short duration may be prolonged by injecting a few drops of a strong silver nitrate solution at the point of puncture so as to produce a continuous irritation. The polyuria following puncture of the medulla is believed to be due to a local dilatation of the renal vessels caused by nervous impulses which reach the kidneys through the splanchnic nerves. According to the recent work of Jungmann, this nervous polyuria, which may be induced either by puncture of the medulla or by section (irritation) of the splanchnic nerves, is associated with an increased elimination and concentration of sodium chlorid in the urine. It has, therefore, been spoken of as a sodium chlorid diabetes. In this respect it differs from the polyuria of diabetes insipidus, for in that condition, as we shall see, the concentration of salt in the urine is diminished.

Polyuria and the Hypophysis.—Polyuria may also be produced by experimental lesions of other portions of the brain. Operations upon the hypophysis and injuries to its immediate neighborhood are not infrequently followed by polyuria. Considerable discussion has arisen as to whether this diuresis is due to nervous influences acting upon the kidney or to the liberation of an internal secretion from the hypophysis. Schäfer showed that extracts of the posterior lobe of the pituitary gland possess marked diuretic properties. The diuresis following their injection continues for some time and it is often associated with an increase in the volume of the kidney. According to Cushing, a subcortical transplanta-

tion of the posterior lobe of the hypophysis at times causes polyuria which ceases when the transplanted lobe is excised. Such an experiment indi-

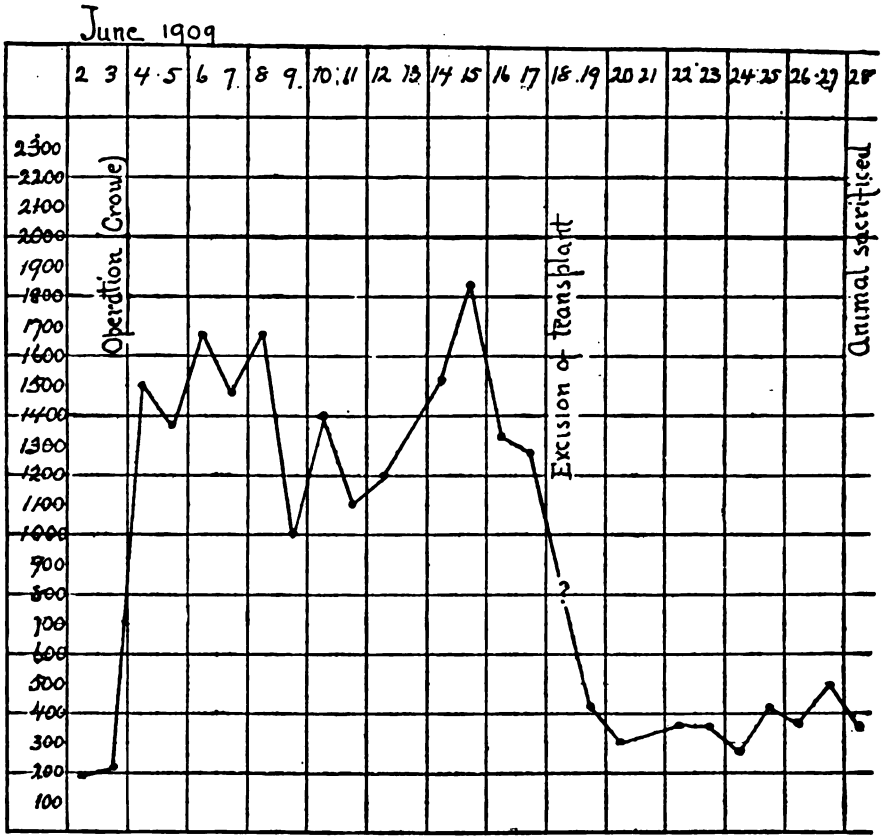

Fig. 84.—Chart Showing Polyuria Following Reimplantation of the Posterior Lobe of the Hypophysis in the Cerebral Subcortex After Excision. Polyuria Was Promptly Interrupted After Excision of the Transplant. (From Cushing, Boston Med. and Surg. Jour.)

cates that the polyuria of experimental hypophysis injury is not due to direct stimulation of nervous paths, but is caused by an entrance of the posterior lobe secretion into the circulation.

Diabetes insipidus

In diabetes insipidus unusually large quantities of dilute urine are habitually passed. This contains neither albumin nor sugar. Five to ten liters daily, with specific gravities ranging from 1.003 to 1.010, are not uncommon. The total solids eliminated during the day are normal and depend upon the character of the diet. Not infrequently, relatively large quantities of urine are excreted during the night (nycturia).

Furthermore, when extra quantities of liquids are given there may be an unusual delay in their elimination. These evidences of slow elimination of liquids are, however, neither constant nor characteristic of the disease.

Patients suffering from diabetes insipidus habitually drink excessive quantities of water and the question naturally arises: is the condition primarily one of increased thirst and polydipsia with secondary polyuria, or is it due primarily to an excessive secretion of urine which causes a secondary thirst through an impoverishment of the body in water? It seems certain that either of these conditions may occur in man. The former is spoken of as a primary polydipsia, the latter constitutes diabetes insipidus in the more restricted sense. It is not always easy to distinguish cases of primary polydipsia from cases of true diabetes insipidus. The distinction is based mainly upon the results which follow a forced restriction of the liquid intake. As a result of such restriction, the urine of a patient with primary polydipsia approaches that of a normal individual in quantity and in concentration. The urine of the patient with true diabetes insipidus, on the other hand, though lessened in amount, does not, as a rule, become as concentrated as normal urine, while solids are retained in the body and the blood may show an abnormal increase in its molecular concentration.

Diabetes insipidus must also be distinguished from those cases of chronic nephritis where large quantities of dilute urine are passed. Occasionally such patients show little or no albumin in the urine and the clinical differentiation is not simple. That the two are essentially different, however, is evident (1) because diabetes insipidus is not a fatal disease, (2) because patients with diabetes insipidus rarely develop nephritis, and (3) because no evidence of nephritis is ordinarily found at autopsy.

The most characteristic feature of diabetes insipidus is the fact that the concentration of the urine remains low in spite of measures which ordinarily raise it. In severe cases and with a free allowance of water, the administration of sodium chlorid to such patients results in an increased secretion of dilute urine. In this way the extra salt is eliminated from the body. Similarly, when meat is given the amount of urine is increased but its concentration is not greatly changed and in this way the extra nitrogenous waste is excreted. (See Fig. 85). Conversely, the amount of urine may be reduced by a diet containing small amounts of salt and protein. If liquids be withheld there may be a diminution in the amount of urine but its concentration is not increased to the same degree as it would be in a normal individual under similar circumstances. The insufficient elimination of solids from the body may raise the molecular concentration of the blood and the patient suffers from intense thirst.

Patients with diabetes insipidus show at times disturbances in per-

spiration. Their skins often appear unusually dry and when exposed to heat they may not perspire as profusely as does the normal individual. The cause of this diminished sweating which is seen in some but not in all patients suffering from diabetes insipidus is not understood. According

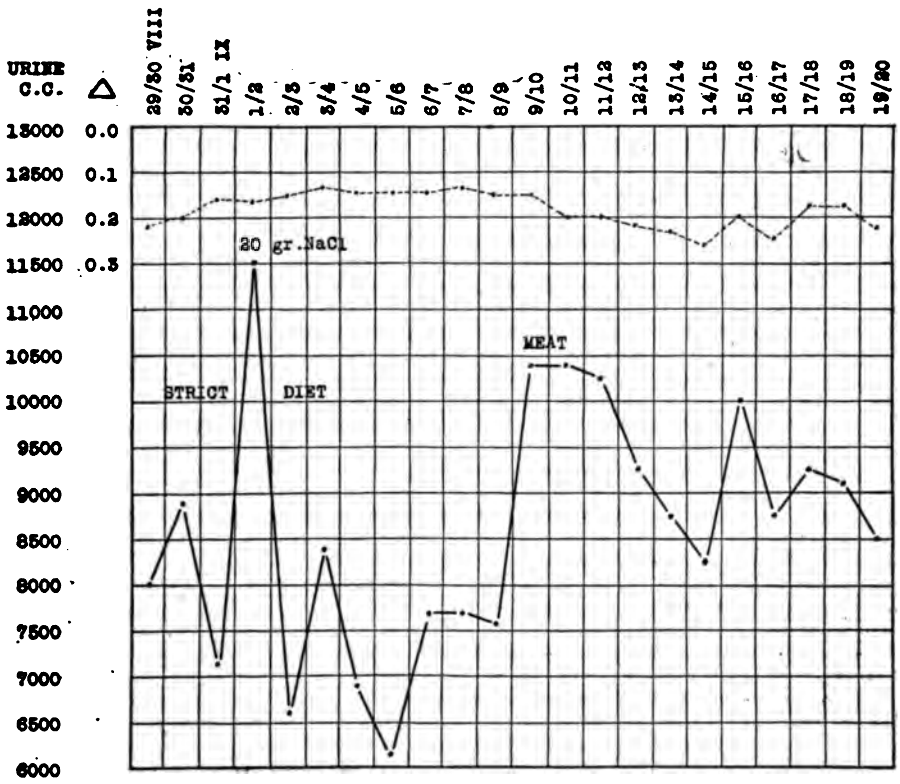

Fig. 85.—Diabetes insipidus. Continuous Line Represents the Amount of Urine Daily. Broken Line Represents the Molecular Concentration As Determined By Its Freezing Point (Δ). During the Strict Diet Which Contained Little Salt and a Minimum of Protein the Amount of Urine Was Reduced. The Addition of Salt or of Meat to the Diet Increased the Quantity of Urine Without Causing a Marked Change in Its Molecular Concentration. (Drawn from E. Meyer, Deutsch. Arch. f. klin. Med.)

to some it is due to a drying out of the body from excessive urination. According to others it is coördinate with or possibly even primary to the polyuria.

The exact mechanism in diabetes insipidus is still under discussion. Erich Meyer believed that the essential disturbance is an inability on the part of the kidney to secrete a concentrated urine. As a result of this inability large quantities of liquid must be excreted in order to carry away in dilute solution the nitrogenous wastes, the sodium chlorid and the other solids which are eliminated by way of the kidneys. The amount of urine is, therefore, determined by the quantity of solids which must be

excreted. Since a low protein and low salt diet furnishes less solids it leads to a diminution in the amount of urine. According to the view of Forschbach and Weber, on the other hand, diabetes insipidus may be due essentially to a primary increase in the output of water. Diuresis is produced with abnormal ease and the low concentration of urine is a secondary manifestation. The concentration of the urine, though low, is not fixed and may be made to show as marked fluctuations, though at a lower level, as does normal urine. When liquids are restricted and salts or urea given, the concentration of the urine may be raised and the specific gravity may for a short time reach 1.020 or higher. In such an experiment, however, the concentration of sodium chlorid and other molecules in the blood may rise above the normal, as is seen in the following chart.

	Blood Examination for	Water ad lib.	Thirst + NaCl
Diabetes insipidus......... Case I..................	δ NaCl	-0.57 0.56%	-0.69 1.03%
Diabetes insipidus......... Case II...............	δ NaCl	-0.57 0.56%	-0.64 0.66%
Control..................	δ NaCl	-0.56 0.62%	-0.59 0.61%

Effect of thirst plus administration of sodium chlorid upon the reduction of freezing point of blood (δ) and the percentage of sodium chlorid in serum. (From Socin.)

It would seem, therefore, that a relative rather than an absolute inability to concentrate the urine is the characteristic change.

The primary cause of diabetes insipidus does not lie in the kidney itself. Pathological examinations of the kidney are practically negative and no definite association with other renal diseases occurs. On the other hand, evidence is constantly accumulating in favor of the view that diabetes insipidus is frequently associated with diseases of the central nervous system. We have already mentioned that a transient polyuria can be produced by injury to certain portions of the medulla oblongata. The polyuria resulting from such experimental injuries, however, is associated with a normal or an increased concentration of sodium chlorid in the urine and in this respect it differs essentially from the diabetes insipidus of man. Furthermore, it is uncommon to find lesions involving this region of the brain in cases of diabetes insipidus.

On the other hand, a number of cases of diabetes inspidus have recently been reported which were associated with disease of the pituitary gland. The older literature also contains many cases in which on account of optic atrophy, obesity or delay in sexual development one might well

assume the presence of pituitary disease. Many cases of diabetes insipidus are also associated with cerebral syphilis, especially at the base of the brain. Such lesions might easily disturb the secretion of the pituitary gland. Brilliant therapeutic results have been obtained in several such patients by antisyphilitic treatment. The relation to the nervous system is also apparent in the remarkable reduction in the output of urine with an increase in the specific gravity which followed lumbar puncture in the case of J. B. Herrick. Finally, as we have seen, experimental injuries to the gland or its neighborhood may be followed by marked polyuria and where the posterior lobe has been transplanted this polyuria may cease when the transplanted lobe has been removed. Matthews has produced a long-continued polyuria by introducing a foreign body into the region of the posterior lobe and Frank has reported a similar clinical case in which a bullet lodged in the pituitary fossa. Since the cells of the posterior or the intermediary lobe contain a diuretic substance the hypothesis seems justified that diabetes insipidus, in some cases at least, is due to an excessive escape of this diuretic substance into the circulation. Whether all cases will eventually be shown to be due to pituitary disease is as yet uncertain.

Oliguria—Anuria

A diminished quanity of urine may be due to a number of causes. Among these are a reduction in the amount of water available for urinary secretion, disturbances in the renal circulation and diseases of the renal cells.

Oliguria from Lack of Water.—Lack of available water may be due to a diminution in the amount of water taken by mouth or to an increased excretion of water through channels other than the kidneys. It is common knowledge that the urinary secretion is reduced when one drinks little water or when on account of excessive perspiration, constant vomiting, or severe diarrhea unusual quantities of water are lost from the body. Such conditions cause not only a diminution in the urine but they increase its concentration. Waste materials are usually removed to a normal degree and the molecular concentration and reaction of the body tissues are usually not changed. Only in very severe choleriform diarrhea is the molecular concentration of the body fluids altered.

Oliguria from Poor Renal Circulation.—A second cause for a diminution in the secretion of urine is an interference with the circulation of the blood through the kidneys. In heart disease this may occur owing to a general slowing of the circulation. It may also be due to an obstruction of the renal veins by the pressure of tumors or collections of fluid in the abdomen. Finally, it may be due to spasm of the arteries or arterioles in the kidney as in the acute stages of severe strychnin poisoning.

Oliguria in Nephritis.—The urine is frequently diminished in acute nephritis and in certain forms or stages of chronic nephritis. This oliguria may be due to various causes. Changes in the secretory activity of the renal cells and blocking of the tubules by cellular detritus seem responsible for the diminished secretion in certain forms of kidney affections. On the other hand, it seems certain that oliguria or anuria may also be due to secondary circulatory changes. A constriction of the renal blood vessels reduces the blood flow and diminishes the output of urine. According to Schlayer, oliguria in experimental nephritis is always associated with a demonstrable reduction in the vascular reactions of the diseased kidney. Finally, since the kidney is enclosed within a rather unyielding capsule, any marked swelling of the renal parenchyma might interfere with the renal circulation by reason of the increased intrarenal tension.

The diminution in urine produced by heart disease and by nephritis differs from that produced by thirst or loss of water from the body in that it is associated with the retention of water and other urinary constituents within the body. As a rule, sodium chlorid and water are retained together so that the osmotic relations within the body are not seriously altered. The questions whether the retention of salt or that of water is primary and whether such retentions are due primarily to renal disease or to changes in other tissues will be discussed elsewhere (page 437). It may be said in passing, however, that the retention of water and salt in the body is not necessarily attended by other evidences of disturbed renal function.

Renal Decapsulation.—Remarkable results sometimes follow decapsulation of or incision into a nephritic kidney. The exact value of decapsulation as a therapeutic procedure and the class of cases most suitable for this operation are still being discussed. It would seem, however, that the most brilliant results have been obtained in acute nephritis or in acute exacerbations of chronic nephritis associated with renal hemorrhage, edema, anuria or uremia. Following an operation on such patients there may be an almost immediate increase in the amount of urine excreted with relief from threatening symptoms.

It is generally conceded that the favorable results which follow renal decapsulation or nephrotomy are to be attributed mainly to changes in the circulation of the kidney. Especially in acute nephritis or in chronic nephritis associated with edema and anuria the kidneys often appear to be under considerable tension. By stripping back the capsule the tension is relieved and the circulation through the kidney is improved. Reginald Harrison, who was one of the first to advocate the surgical treatment of nephritis, compared such a kidney to a glaucomatous eye and attributed the beneficial results of the operation to the relief of tension. Edebohls sought to extend the use of decapsulation. He believed that the circula-

tion of the kidney was also improved by the entrance of new blood vessels through the new capsule. Experimental studies have shown, however, that an efficient collateral circulation rarely if ever follows decapsulation of the kidney. A new capsule is rapidly formed and ultimately this may furnish a poorer blood supply to the kidney than the original capsule. Decapsulation during the quiescent stages of chronic nephritis is now rarely advocated by surgeons, and little can be expected in such cases. It has proved of value mainly in cases with edema and threatening anuria and in cases with nephritic pain or hemorrhages.

Anuria

In anuria the urinary output is reduced to zero. Anuria may be due either to a failure on the part of the kidney to secrete urine or to an obstruction in the urinary passages which prevents the excreted urine from escaping and eventually checks the renal function. It is unnecessary to enumerate all the causes of obstructive anuria. Among the more important are bilateral calculi, malignant tumors, and obstruction of a ureter when there is but a single functioning kidney. Anuria sometimes complicates acute nephritis, particularly that due to acute bichlorid poisoning.

Nervous Anuria.—In not a few cases of anuria even of several days' duration no mechanical explanation for the anuria has been found and the explanation usually offered is that the anuria is of a nervous character, being either reflex or hysterical. It is well known that the secretion from a kidney is influenced by reflexes which may arise from manipulations of the corresponding ureter. As a result of such reflexes there may be an increased or a decreased secretion of urine. In some cases when the ureter has been firmly tied, urinary secretion in inhibited from both kidneys and this anuria may last for five or six hours or more. Similarly, not a few cases have been reported in which changes in one ureter, especially those produced by stone, have caused complete suppression of urine, although the kidney on the opposite side was apparently normal. Charcot and others have also reported remarkable cases of anuria persisting over long periods of time which were attributed to hysteria. In some of these cases the anuria is said to have lasted from ten to twenty days with no apparent serious consequences. One may well doubt such extraordinary reports; at least until they have been supported by modern methods and the blood has been shown to contain excessive amounts of urinary material. On the other hand, the briefer anurias of reflex or hysterical origin may well be due to spasm of the smaller arterioles in the kidneys. In some of these cases it is possible that an acute edema of the kidney similar to angioneurotic edema may cause the anuria through compression of the kidney.

Manifestations of Anuria.—Anuria from hysterical or reflex causes is, so far as we know, rarely if ever fatal. Sooner or later the flow of urine is reëstablished. Anurias due to bilateral obstruction of the ureters and to acute nephritis frequently continue until death. The usual duration of life under such circumstances is from eight to fourteen days, but complete anurias of twenty days or even more have been reported.

During the earlier days of a complete anuria the symptoms are surprisingly few. As time goes on the patient often complains of headache, fatigue and weakness. The breath develops a urinous odor. Respirations become deeper. There may be muscular twitchings but general convulsions are rare. Toward the end the patient becomes somnolent and may die rather suddenly or after a brief coma. The symptoms of complete anuria resemble those which are present in nephritic patients who show a marked increase in the non-protein nitrogen of the blood.

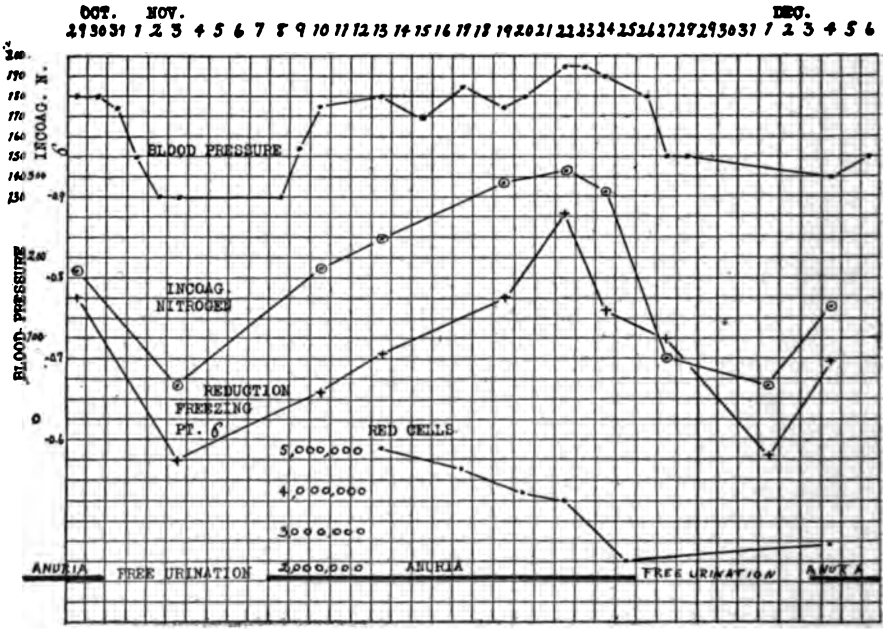

Fig. 86.—The Effect of Intermittent Anuria Due to Malignant Disease Upon the Blood and the Blood Pressure. Anuria Began About Oct. 22 and Lasted Through Oct. 30. This Was Followed by Free Urination and by Two Subsequent Periods of Anuria in the Last of Which the Patient Died. In Addition to the Changes of Blood Pressure, Note the Increase of Incoagulable Nitrogen with Each Retention. The Developing Anemia Is Probably Due in Part to Hydremia. (Drawn from a case reported by Brasch, Deutsch. Arch. f. klin. Med.)

The molecular concentration of the blood, as indicated by lowering of the freezing point, increases during anuria and there is also a marked increase of the non-protein nitrogen of the blood. A retention of water

with dilution of the blood and a rapid fall in the red blood corpuscles may also occur. As a rule, marked edema is absent. The blood pressure rises, but not to excessive heights, for pressures above 180 mm. of mercury are rare in cases of complete anuria. These changes are well shown in Figure 86, which has been constructed from Brasch's report of a case of intermittent anuria due to malignant disease.

Albuminuria

Physiological Albuminurias

Practically all urines contain minute traces of albumin which can be demonstrated by special methods. Albuminuria in the clinical sense, however, is a condition in which albumin may be detected in the urine by the tests in common use, particularly the heat and nitric acid test, Heller's ring test, and the potassium ferrocyanid and acetic acid test. Even with these, albuminurias occur under more or less physiological conditions. The albumin may be derived from admixtures of seminal or vaginal secretions, or from a diseased bladder, ureter or urethra. Of more interest, however, are those cases in which the albumin comes from the kidney.

Alimentary Albuminuria.—When a foreign protein is introduced into the body by other routes than the alimentary tract, it frequently happens that a portion is excreted in the urine and can be recognized by biological tests. Proteins taken with the food, on the other hand, do not ordinarily cause albuminuria. They are usually broken down during the processes of digestion and their constituent building stones are absorbed. After absorption these latter may be reconstructed into the body proteins or they may undergo still further disintegration. Under certain circumstances proteins may pass unchanged through the intestinal wall and thus enter the body as foreign substances. They may be recognized in the blood by biological tests and they may also be excreted by the kidneys and identified in the urine. Ascoli, for example, found that it was possible in certain healthy individuals to produce an egg white albuminuria by giving very large doses of egg white. Such an alimentary albuminuria depends more upon the permeability of the intestinal mucosa than upon changes in the kidneys. In infants who have in general a more permeable intestinal mucous membrane, alimentary albuminuria is more readily produced and especially is this true in inflammatory conditions of the gastrointestinal tract. In adults alimentary albuminuria appears to be quite uncommon.

Albuminuria from Exercise.—Albuminuria may also be produced in normal individuals by violent exercise. Thus, after rowing races, football games, or long distance running contests, albumin is present in the

urine of almost every contestant. The quantity may be very large and it may be accompanied by numerous casts and red blood cells. Ordinarily these urinary changes disappear in a day or two after the contest but they may continue for weeks or even longer in exceptional cases.

Urinary Findings Before a Marathon Race, Immediately After and at Subsequent Periods (From Barach)

	No. of Cases	Albumin	Blood	Casts	Aceton Bodies
Before	24	1	0	0	0
Immediately after	19	19	18	19	18
One week subsequent	19	4	0	6	0
Three weeks subsequent	..	3	0	3	0

It is not possible to establish any quantitative relation between the amount of exercise and the occurrence or amount of albuminuria. There appear to be very considerable individual variations.

Albuminuria from Cold.—Albuminuria may also follow exposure to cold and particularly prolonged exposure with marked chilling. Apparently a brief exposure to cold with a good reaction as in hydrotherapeutic treatments does not ordinarily cause albuminuria.

Orthostatic Albuminuria—Lordotic Albuminuria.—By far the most important and the most interesting type of so-called physiological albuminuria is that which is variously known as cyclic, postural, or orthostatic albuminuria. In this condition the urine is free of albumin when the patient is lying down, but when he stands albumin appears. A daily cycle is, therefore, established. The urine secreted during the night contains no albumin. It appears in that excreted after rising and usually reaches a maximum sometime before noon. In the afternoon it is present in smaller amounts. It has been shown that this albuminuria depends not upon exercise but upon the upright posture, for it is not present if the patient exercises while lying down. In a majority of cases this albumin is serum albumin. Usually no casts appear, although a few hyaline or granular forms may be present. Orthostatic albuminuria is found particularly in adolescents between the ages of fifteen and twenty-one and its frequency during these ages has been variously estimated by different observers. According to Lommel, for example, it is present in about 19 per cent of such individuals.

Persons suffering from orthostatic albuminuria usually present no other symptoms referable to the kidneys. Many of them are of a delicate slender build, and they frequently complain of lassitude or of headache. Physical examination frequently, but not invariably, shows vasomotor and nervous instability.

Prognosis.—The prognosis of orthostatic albuminuria has been much discussed. Certain authors, notably Senator, have been inclined to attribute most of these cases to an inflammatory irritation of the kidneys and consequently have advised extreme caution in giving a prognosis. It is certain that cases of true nephritis may during their milder or declining stages show an intermittent albuminuria which depends upon the posture of the individual and in a given individual it may not always be easy to exclude the possibility of a mild or disappearing nephritis. On the other hand, numerous observers have testified to the fact that by far the largest proportion of young individuals with orthostatic albuminuria never develop a definite nephritis and that in later life they lose the tendency toward albuminuria when standing.

Pathogenesis.—In such patients, therefore, some explanation other than a mild nephritis is sought. It has been suggested for example that this form of albuminuria may be due to changes in the permeability of the cells lining the urinary passages and particularly to changes in the glomeruli, so that albumin is not held back by the renal filter as it normally should be. This suggestion does not seem to be susceptible of proof.

According to another group of hypotheses, orthostatic albuminuria depends upon changes in the renal circulation. Erlanger and Hooker, who studied very carefully the blood pressures in a patient with orthostatic

Fig. 87.—Normal Lordosis in a Boy 12 Years Old. (From Jehle, "Ergebn. d. inn. Med. u. Kinderheilk.," published by J. Springer, Berlin.)

Fig. 88.—Excessive Lordosis in a Boy 12 Years Old. (From Jehle, "Ergebn. d. inn. Med. u. Kinderheilk.," published by J. Springer, Berlin.)

Fig. 89. — Excessive Lordosis in a Young Girl. (From Jehle, "Ergebn. d. inn. Med. u. Kinderheilk.," published by J. Springer, Berlin.)

albuminuria, found no relation between the albuminuria and the absolute height of the blood pressure. On the other hand, they found that in their

patient the difference between systolic and diastolic pressures was less than the normal. This difference, the so-called pulse pressure, normally lessens when a person assumes the standing position. It was also lessened when the patient with orthostatic albuminuria assumed an upright position. They suggested, therefore, that the albuminuria might depend upon the unusually small pulse pressure in their patient. Recently Gesell has shown that a diminished pulse pressure experimentally induced in animals may increase an albuminuria. On the other hand, Bass and Weissler have failed to establish any relation between blood pressure and orthostatic albuminuria.

Fig. 90.—The Same Girl As in the Previous Figure, Showing Correction of the Lordosis by Placing One Foot on a Stool. In This Position the Albuminuria Previously Present Disappeared. (From Jehle, "Ergebn. d. Inn. Med. u. Kinderheilk.," published by J. Springer, Berlin.)

Jehle has pointed out that patients with orthostatic albuminuria usually show an unusual anterior curvature of the spine in the region of the twelfth dorsal to the second lumbar vertebrae and he has attempted to prove that this lordosis which appears when these patients assume the standing position is responsible for the albuminuria. He found that it was usually possible to cause an albuminuria even when these patients were lying down, if the lordosis which occurred naturally in the standing position were reproduced artificially by placing props beneath the lumbar region. Furthermore, the albuminuria could be made to disappear when the patient was standing if the lordosis were corrected either by mechanical means, such as a jacket or brace, or by a corrective posture, e. g., placing one foot on a chair. In spite of considerable controversy concerning Jehle's views, it is generally admitted that albuminuria from lordosis does occur. Just what proportion of cases of orthostatic albuminuria will be shown to be due to this cause is still uncertain. Jehle believes that while vasomotor influences may play a part in the etiology of orthostatic albuminuria the most important factor in practically all cases is the mechanical effect of the lordosis. Presumably this acts by interfering with the return of venous blood from the kidney owing to some kink or compression of the renal veins.

Pathological Causes of Albuminuria

Albumin in the urine may be derived either from the kidneys or from the urinary passages. When it comes from the latter it may be caused by inflammations or by hemorrhage. In such cases, as a rule, the amount of albumin is relatively small compared to the number of leukocytes or of

red cells. It differs in this respect from the albuminuria of kidney diseases, for in the latter the albumin is usually abundant when compared with the number of cells.

Albuminuria from Circulatory Disturbances.—Circulatory disturbances in the kidney may cause albuminuria. Even a brief interruption of the blood flow by ligature of the renal artery or veins produces this effect. Albuminuria is also common in the severe passive congestion of cardiac decompensation. It seems probable that as a result of a temporary stoppage or a long-continued slowing of the blood stream there is a change in the nutrition of the renal cells which renders them more permeable to albumin. We have seen that according to prevailing views orthostatic albuminuria is due to circulatory changes in the kidneys, which consist either in a diminished pulse pressure or in a mechanical interference with the venous outflow as a result of lordosis.

Albuminuria from Kidney Disease.—The most common and most important cause of albuminuria is disease of the kidneys themselves. The nephropathy may either be degenerative or inflammatory in character. The albumin in the urine is derived almost entirely from the proteins of the blood plasma, serum albumin passing through the renal membranes in larger quantities than serum globulin. As a rule, the largest amount of albumin seems to pass through the glomeruli but some may be derived from the kidney tubules.

Cylindruria

In many diseases of the kidney casts and cylindroids appear in the urine. The relation between these two is not definitely established but it seems certain that no absolutely sharp line can be drawn. Many cylindroids are derived from the kidney, for transitions between casts and cylindroids are frequently found in the urine and patients who on some occasions show typical casts will on others show only cylindroids. In general, however, the presence of cylindroids seems to have a less serious significance than the presence of casts.

Origin.—Two views have been advanced as to the origin of casts. According to the first, the albumin which has passed the renal filter becomes coagulated in the renal tubules. According to the second view, casts are made up from cellular detritus which has been derived from the products of degenerative changes in the epithelium lining the tubules. Clinical observations have demonstrated that there is no constant relation between the degree of albuminuria and of cylindruria. Albuminuria with few casts is not uncommon, especially in circulatory affections of the kidneys. Cylindruria without albuminuria also occurs, particularly following the administration of salicylates and during constipation. In diabetic coma the number of casts is much greater proportionately than the amount of albumin. We have seen that the albumin enters the urine mainly

through the glomeruli and the fact that albuminuria and cylindruria are frequently dissociated suggests that casts may be derived from changes in the tubules. Experimental studies have, in fact, shown that casts occur particularly after extensive degenerative changes in the tubular epithelium. According to R. M. Smith, granular casts are due to a rapid formation and excretion while hyaline casts are formed and excreted slowly. The showers of casts which appear at times seem to be due to a rapid washing out of casts which have already formed.

Experimental Nephritis

Types of Experimental Nephritis.—It has been known for some time that the injection of various poisons into animals will produce renal changes. Certain substances, particularly the chromium salts, the uranium salts, mercuric chlorid and the tartrates, cause extensive necroses of the epithelium lining of the urinary tubules. According to Suzuki, each of the first three of these poisons affects specific portions of the proximal convoluted tubules. On the other hand, cantharidin, arsenic and snake venom cause albuminuria, hematuria and anuria with anatomical changes mainly in the glomeruli. From the anatomical standpoint, therefore, there is a division into epithelial and vascular renal poisons. This distinction is never an absolute one. Cantharidin also produces cloudy swelling and formation of vacuoles in the proximal convoluted tubules, while glomerular changes have been described in uranium nephritis by Christian and by Baehr.

Of particular interest are studies of the functions of experimentally diseased kidneys, on account of the light which such studies throw on the problems of human nephritis. Schlayer and his associates studied the urinary elimination and the vascular reactions of normal and diseased kidneys. They tested the reaction of the renal vessels to reflexes from sensory stimuli (tobacco smoke blown into the nose) and to adrenalin, each of which normally produces a transient diminution of kidney volume with an increase in general arterial pressure. Caffein and strong salt solution were used for testing the reaction to influences which normally dilate the renal vessels. From their experiments they concluded that in the mild or moderately severe forms of tubular nephritis produced by potassium bichromate the vascular reactions were normal. Only in the later stages of this type of nephritis was there a marked reduction of diuresis and loss of the vascular reactions. After the administration of cantharidin or arsenic, on the other hand, the general blood pressure was low and the vascular reactions were altered, being excessive in the very mild cases and diminished or lost in the more severe cases. On the basis of these experiments Schlayer has distinguished two experimental types of

nephritis. In the tubular form no marked changes occur in the vascular reactions while in the vascular form the vascular reactions are at first increased, later diminished and finally abolished. The experimental nephritis produced by uranium seemed to occupy an intermediary position, because in this type there were not only tubular degenerations and necroses but early alterations in the reactions of the blood vessels. These observations have been confirmed in the main by R. M. Pearce and his associates, although these authors were unable to establish equally sharp distinctions between the two types of nephritis.

Relation Between Diuresis and Vascular Reactions.—We have stated that in the very mild forms of vascular nephritis the vascular reactions may be more marked than the normal, whereas in somewhat more severe forms the reactions are diminished and eventually they are lost. According to Schlayer, the amount of urine secreted is directly proportioned to the irritability of the renal blood vessels as measured by the degree of vascular reaction. When the reactions are excessive polyuria is present. Polyuria, therefore, may represent a mild degree of vascular injury. When the reactions are less marked than normal there is oliguria, and when the reactions are absent, anuria. Schlayer's contention that anuria is associated with an absence of vascular reactions has not been confirmed by certain of the later investigators (Pearce, MacNider).

The Excretion of Lactose and Potassium Iodid.—Schlayer also found that damage to the renal tubules interfered with the excretion of sodium chlorid and he concluded that an inability to excrete sodium chlorid was characteristic of tubular lesions. From experimental studies, therefore, it would appear that severe vascular lesions diminish the excretion of water and that tubular lesions diminish the excretion of sodium chlorid. Inasmuch as both sodium chlorid and water are normal body constituents and their excretion through the kidney is influenced by factors outside of this organ, Schlayer tested the excretion of other substances not normally present in the body, with the hope that these might serve to indicate the separate functional capacities of the tubules and of the renal blood vessels (glomeruli). He found that in experimental nephritis of the vascular type the excretion of lactose is interfered with, whereas in experimental nephritis of the tubular type the excretion of potassium iodid is delayed. He, therefore, advocated that the rate of excretion of these substances be used clinically as tests of the functional damage to the vascular and tubular apparatus in human nephritis.

The clinical value of Schlayer's functional kidney tests with potassium iodid and lactose has not been definitely settled. A number of studies have been made in which the results of these tests were compared with other functional disturbances present in nephritic patients, and in particular they have been compared with the occurrence of nephritic edema and with the retention of nitrogenous waste products in the body. Nephritic edema,

as we shall see (page 430), is usually associated with an imperfect elimination of sodium chlorid. Comparative studies of the elimination of sodium chlorid and of potassium iodid by nephritic patients have shown that there is a general parallelism between the two and that patients who show a deficient elimination of the one usually show a deficient elimination of the other. Furthermore, in a single patient an improvement in the elimination of the one is usually accompanied by a simultaneous improvement in the elimination of the other. The parallelism, however, does not seem to be an absolutely strict one and some patients eliminate one poorly while eliminating the other well. It would seem, therefore, that the elimination of potassium iodid is not an absolutely trustworthy indicator of the ability of the body to eliminate sodium chlorid and that as a practical guide for instituting a low salt diet it is not altogether dependable.

The use of intravenous lactose injections, as recommended by Schlayer, yields results which are more or less parallel to those furnished by studies of nitrogenous retention. Here again, however, the parallelism is not an exact one and the rate of lactose elimination cannot replace estimations of the non-protein nitrogen in the blood. The excretion of lactose is relatively delayed in many cases of nephritis and it is possible that this test may prove of value as a very sensitive indicator of slight renal damage. From the practical standpoint, however, such injections are objectionable because they, like other intravenous injections, may be followed by violent febrile reactions unless scrupulous care be taken to avoid the so-called water fever (see page 483).

Relation of Functional to Anatomical Changes.—Even though the results obtained by these tests may fail to correspond with the occurrence of nephritic edema and with the retention of non-protein nitrogen in the body, they may still, as Schlayer believes, indicate the functional activity of different portions of the renal substance. While in general the functional tests correspond with anatomical changes in experimental nephritis, there are even here discrepancies, for in the experimental nephritis produced by uranium salts there may be a marked functional insufficiency of the vascular apparatus with relatively slight changes in the appearance of the blood vessels and glomeruli.

As yet but few autopsies have been reported on nephritic patients who have been subjected to Schlayer's tests, but these also show that it is difficult to correlate the chief anatomical lesions and the chief functional deficiencies. Here, as elsewhere, the explanation is always possible that functional changes occur without demonstrable anatomical lesions.

In view of the fact that we are still very uncertain as to the normal functions of renal tubules and glomeruli, it seems better for the present to discuss kidney disease not from the standpoint of deficiencies in these particular parts of the kidney but from the standpoint of deficiencies in the elimination of substances normally excreted, without regard to the

portion of the kidney involved. A discussion from this standpoint is further justified by the fact that retentions of sodium chlorid or of nitrogen waste are associated with definite symptoms and that they furnish valuable data for prognosis and therapy.

Retention of Nitrogenous Waste Products

The catabolism of proteins in the body leads to the formation of simpler nitrogenous compounds which are distinguishable from proteins by the general fact that they are not so readily precipitated by various reagents. The amount of these substances is estimated by determining the nitrogen content of a body fluid after the proteins have been precipitated and removed by filtration. This nitrogen is spoken of as the non-protein or incoagulable nitrogen.

Nitrogenous Excretion in Nephritis

For the most part the nitrogen waste of the body is finally converted into urea and is eliminated as such by the kidneys. The amount of urea appearing in the urine depends primarily upon the amount of nitrogenous material taken in the food, for the body has but a limited storage capacity for nitrogenous compounds and promptly excretes any excess. It is evident, therefore, that no conclusion concerning the function of the kidneys can be drawn from simple estimations of the urea or total nitrogenous output in the urine. The excretion must always be compared with the intake. Even though both intake and output are determined it may be difficult or impossible to recognize nitrogenous retention, for it is evident that small differences between intake and output might in the long run lead to very marked accumulations of waste nitrogen in the body and that even when the intake and output balanced there might be either a low or a high level of waste nitrogen already in the body.

When the nitrogenous intake and output are carefully followed in cases of chronic nephritis temporary discrepancies are not infrequently found between the two. At certain times there may be a nitrogen retention, while at other times the nitrogen losses exceed the intake. The nephritic kidney frequently does not accommodate its excretion of nitrogenous substances to the dietetic intake with the same precision that is common in healthy individuals. The degree of accommodation may be tested by giving to patients in nitrogenous equilibrium a certain amount of urea and determining the promptness with which this excess is eliminated. In such experiments, von Monakow found that normally the excessive nitrogen from 20 g. of urea is eliminated within one and a half days. Among patients with nephritis, the elimination of the excessive nitrogen varies. In some patients it is normal, in others it is delayed, while in the

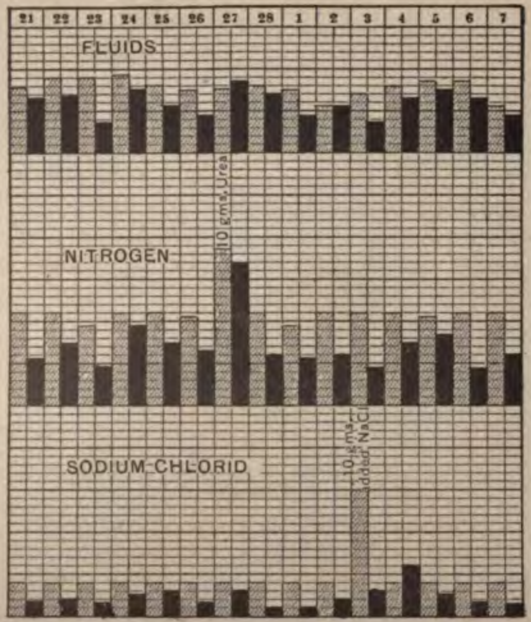

Fig. 91.—Chronic Nephritis. Table Showing the Intake and Urinary Output of Water, Nitrogen, and Sodium Chlorid. The Intake Is Indicated by the Hatched Columns, the Output by the Solid Columns. Note that When 10 Grams of Urea Were Taken, the Excessive Amount of Nitrogen Was Almost Entirely Eliminated on the Same Day. The Patient Was on a Low Sodium Chlorid Intake and the Addition of 10 Grams Caused Only a Slight Increase in the Output and This Was Greatest on the Day Following the Intake. (From Christian, Frothingham, O'Hare and Woods, Am. Jour. Med. Sci.)

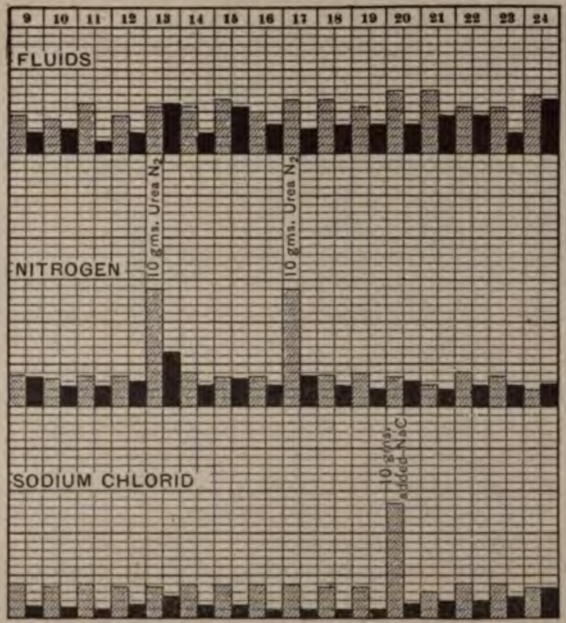

Fig. 92.—Chronic Nephritis. Table Showing the Intake and Urinary Output of Water, Nitrogen, and Sodium Chlorid. The Intake Is Indicated by the Hatched Columns, the Output by the Solid Columns. Note that When 10 Grams of Urea Were Added to the Intake on Two Occasions, the Extra Nitrogen Was Almost Entirely Retained in the Body. Furthermore, the Addition of 10 Grams of Sodium Chlorid Caused Almost No Increase in Its Elimination. (From Christian, Frothingham, O'Hare and Woods, Am. Jour. Med. Sci.)

most severe disturbances the added nitrogen may be almost entirely retained in the body (Figs. 91 and 92).

Non-protein Nitrogen in the Blood

Disturbances in the elimination of waste nitrogen are also indicated by an increased amount of non-protein nitrogen or of urea in the blood. The normal amounts present have been determined by different investigators but the results have varied according to the methods used. By the method of Folin and Denis, strictly normal individuals usually have between 22 and 28 mgms. of non-protein nitrogen per 100 c.c. of blood, of which about 50 per cent (11 to 14 mgms.) is urea nitrogen. Hospital patients show a much wider range, the total non-protein nitrogen varying from 15 mgms. to as much as 40 mgms. without clinical evidence of kidney disease. By the chemically imperfect but extensively used hypobromite method for determining "urea" in the blood, Widal and his coworkers have shown that from 15 to 50 mgms. of hypobromite urea are normally present in 100 c.c. of blood, or expressed in terms of urea nitrogen from 9 to 30 mgms. per 100 c.c.

Among the physiological influences which cause variations in the incoagulable nitrogen of the blood the most important is diet. After a large protein meal there is a distinct increase in the incoagulable nitrogen of the blood, even in a normal individual. Thus Weill records an increase from 21 to 46 mgms. of hypobromite urea after a meal containing about 120 grams of protein. The percentage in the blood is higher when patients are given diets containing large amounts of protein than when the proteins in the diet are restricted. It is probable that a similar rise in the non-protein nitrogen of the blood may be caused by an increased protein catabolism, such as occurs in certain fevers and intoxications. Evidently, therefore, the quantity of non-protein nitrogen in the blood, influenced as it is by the diet, and the rate of protein metabolism, cannot in itself be used as an absolute measure of the efficiency of the kidney in removing nitrogen waste. In order to make accurate comparisons between different individuals it is necessary either that they should be on a standard diet and that the blood should be taken at a given time of the day, or that some comparison be made between the waste nitrogen in the blood and the amount that passes through the kidney into the urine.

Ambard's Formula.—If some relation could be demonstrated between the concentration of urea in the blood and the amount excreted in the urine, this might furnish a basis for measuring accurately the ability of the kidney to excrete this class of waste products. Ambard has, in fact, sought to establish such an exact relationship between the urea of the blood and its excretion in the urine. Unfortunately his calculations were based entirely upon hypobromite determinations, but the principle has been con-

firmed recently with more trustworthy methods by McLean and Selling. According to Ambard, the amount of urea excreted at a given concentration in the urine is directly proportional to the square of its concentration in the blood. When the concentration in the blood is constant the total output in the urine will be greater when large quantities of dilute urine are excreted, the total output being inversely proportional to the square foot of the concentration in the urine. By combining the two laws in a mathematical formula,[1] Ambard believes that he has found a constant which expresses for any kidney the relationship which exists between the concentration of urea in the blood and the total output in the urine. This constant represents the renal efficiency for the excretion of urea and it has been used to measure this function of the kidney (see Fig. 93).

Acute Retentions.—The retention of nitrogenous waste may develop acutely and it may pass off rapidly. In anuria from whatever cause, there is a rapid increase in the non-protein nitrogen of the blood. This is well illustrated in Figure 86, which also shows the rapid return to the normal when the secretion of urine is reëstablished. Similar changes sometimes occur in acute nephritides. Very marked retentions of non-protein nitrogen may develop during the acute stages of nephritis and these may disappear as the renal lesions improve. Thus Reiss reports a case of nephritis after scarlet fever with 283 mgms. of non-protein nitrogen in 100 c.c. of blood which later went on to recovery and a return to normal relations. Similar changes have also been demonstrated in the acute uranium nephritis of rabbits as well as in other forms of experimental nephritis.

Chronic Retentions.—The most important form of nitrogenous retention is that which is encountered in certain cases of chronic nephritis. It is difficult to state how frequently nitrogenous retention occurs in chronic nephritis on account of our uncertainty as to physiological limits. It is probable, however, that slight nitrogenous retentions are by no means infrequent. On the other hand, marked retentions, sufficient to be associated with characteristic symptoms and sufficient to render the prognosis unfavorable, are not very common. According to Widal, an increase in the hyperbromite urea of the blood from the normal upper limit of 50 mgms. to 100 mgms. per 100 c.c. of blood represents a mild to moderately severe retention. When the hyperbromite urea exceeds 100 mgms. a serious condition is always present. In exceptional cases 400 to 500 mgms. or even

[1] Ambard's formula is as follows:

$$K = \frac{Ur}{\sqrt{D.\ \sqrt{\frac{C}{25}}}}$$

Where K is the constant for a given individual.
Ur is the amount of urea in one liter of blood.
D is the output of urea estimated for 24 hours.
C is the concentration per mille of urea in the urine.

more have been found, but such patients usually live only a short time. By Folin's method the total non-protein nitrogen should not exceed 40 mgms. per 100 c.c. It may be increased in nephritis to 300 mgms. or more.

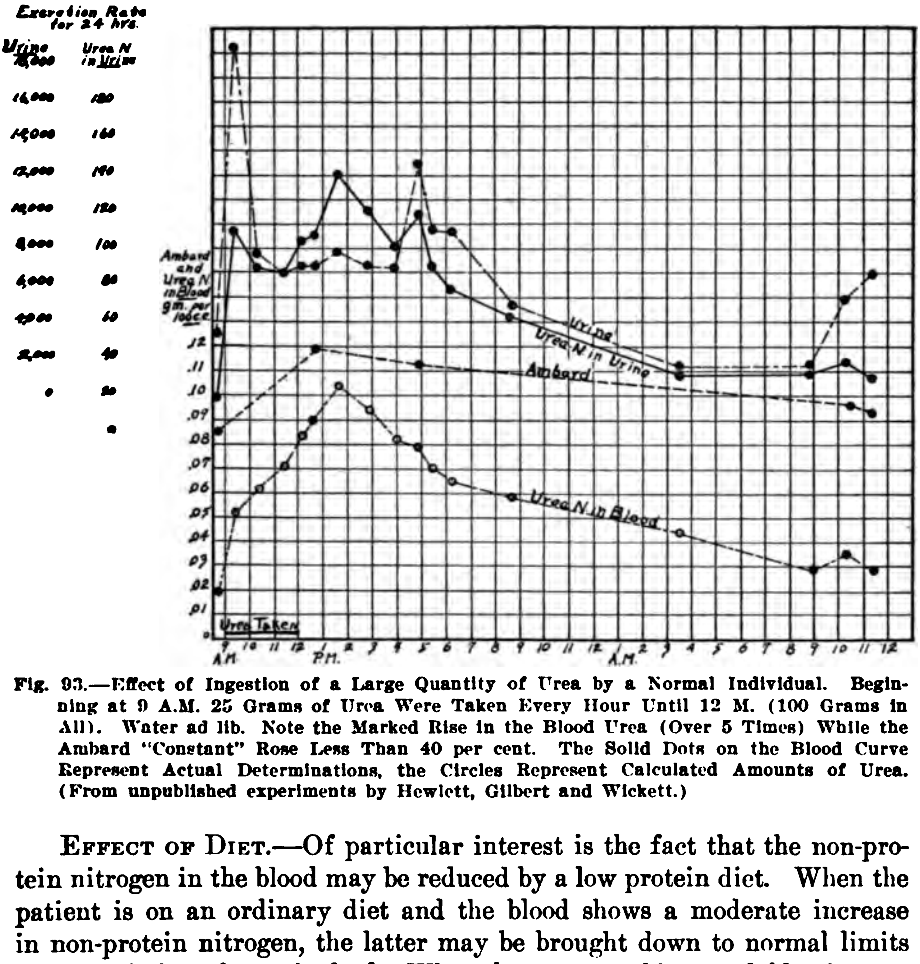

Fig. 93.—Effect of Ingestion of a Large Quantity of Urea by a Normal Individual. Beginning at 9 A.M. 25 Grams of Urea Were Taken Every Hour Until 12 M. (100 Grams in All). Water ad lib. Note the Marked Rise in the Blood Urea (Over 5 Times) While the Ambard "Constant" Rose Less Than 40 per cent. The Solid Dots on the Blood Curve Represent Actual Determinations, the Circles Represent Calculated Amounts of Urea. (From unpublished experiments by Hewlett, Gilbert and Wickett.)

Effect of Diet.—Of particular interest is the fact that the non-protein nitrogen in the blood may be reduced by a low protein diet. When the patient is on an ordinary diet and the blood shows a moderate increase in non-protein nitrogen, the latter may be brought down to normal limits by a restriction of protein food. When the amount of incoagulable nitrogen in the blood is markedly increased, however, even strict dieting will no longer reduce it to the normal concentration. By lessening the protein intake the nitrogenous metabolism may be reduced, but not beyond a certain minimum (see page 231). Whether this minimum in chronic nephritis differs from the normal or not we do not know, but it is suggestive that Mosenthal found variation from the normal protein metabolism in acute experimental uranium nephritis. If the minimum protein requirements of the body are not supplied by the diet then they must be supplied by the body proteins. It is evident, therefore, that the protein metabolism cannot be reduced beyond a certain point by dieting and since in a given

patient the amount of non-protein nitrogen in the blood depends to a large extent upon the rate of protein metabolism, it is evident that there is also a limit to the dietetic reductions of the non-protein nitrogen in the blood. For this reason even the most rigorous restrictions of the protein intake in severe cases of nephritis still leave an excess of nitrogen waste in the body fluids.

Effects of Diuresis.—According to Foster and Davis, the increased non-protein nitrogen in the blood may also be reduced if diuresis follows an abundant intake of fluids. Certain patients with chronic nephritis, even though suffering from an imperfect elimination of nitrogenous wastes, are still able to excrete large quantities of water and in such cases particularly it would appear that the nitrogenous waste may be washed out of the blood by abundant water drinking.

Retention of Individual Nitrogenous Products

Urea.—The urea nitrogen normally makes up about one-half of the total non-protein nitrogen of the blood. Whenever as a result of chronic nephritis there is a marked increase of the total non-protein nitrogen, the urea fraction is relatively high. The proportion of urea nitrogen in the blood may rise moderately (65 per cent of the total) or it may rise markedly (80 per cent and over).

Uric Acid.—We have seen that in gout there is usually an increase in the amount of uric acid in the blood and that this may occur even though the total non-protein nitrogen in the blood is not increased. In nephritis with nitrogenous retention, the amount of uric acid in the blood is also increased and in cases of marked retention it may even exceed the figures usually obtained in gouty patients (page 314). As a rule, however, the proportion of uric acid relative to the total non-protein nitrogen is not great. Myers and his associates believe, however, that many early cases of nephritis, particularly of the interstitial type, give blood pictures which differ little from those of gout.

Creatinin.—The amounts of creatinin and creatin in the blood tend to increase in conditions of nitrogenous retention. Myers and Lough believe that a marked rise in the former is of considerable prognostic significance and indicates an unfavorable outcome.

Other Nitrogenous Bodies.—The amino acid nitrogen of the blood is also frequently increased in conditions of nitrogenous retention, but according to Woods, this increase does not parallel the retention of other bodies. The blood may also show a reaction for indican.

The total non-protein nitrogen in the blood always exceeds to a more or less marked degree the sum of the nitrogen derived from urea, uric acid, creatinin, creatin and amino acids. This excess, which is sometimes called the residual nitrogen, cannot be determined very accurately, for the

reason that any error introduced into any of the preceding determinations influence this figure. Considerable interest is attached to this residual nitrogen, however, owing to the possibility that it may include some unknown bodies which are unusually toxic and which may give rise to toxic symptoms. Woods found that the residual nitrogen was increased in severe cases of retention.

Nitrogen Waste in the Tissues

Urea diffuses readily through the tissues and when the amount of urea in the body is increased excessive amounts are found in most of the tissues. Certain tissues, however, such as fat, bone, cartilage, etc., do not take up much urea. The concentration of urea in the body fluids, such as the spinal fluid and various exudates, is approximately the same as its concentration in the blood. Concerning the distribution of the other nitrogenous products that may be retained in nephritis but little is known.

It has been noted by v. Monokow, Mosenthal and others, however, that a retention of nitrogen in chronic nephritis may not lead to the increase in the non-protein nitrogen in the blood that one would expect if the amount retained were evenly distributed throughout the body. Apparently nitrogenous compounds have been deposited in the tissues. In what form this occurs and whether it is to be regarded as distinctly harmful or as comparable to the retention of nitrogenous material which may occur normally (page 230) is not known.

Symptoms of Nitrogenous Retention

According to Widal, the symptoms associated with nitrogenous retention are loss of appetite, with or without gastric disturbances, fatigue, lassitude, and prostration. These symptoms increase as the retention becomes more severe. In the later stages of retention, the patient becomes somnolent, vomiting and diarrhea may be present, the retinae frequently show the characteristic changes of albuminuric retinitis, itching is common, and there is frequently a marked anemia associated with leukocytosis. On the other hand, general convulsions, prolonged coma, paralyses and other serious or localized nervous manifestations are usually absent.

Relation to Other Renal Functions

Widal, Strauss and others have pointed out on various occasions that in nephritis the different functions of the kidneys may be impaired to different degrees. For example, patients with marked albuminuria, with edema, and with an inability to eliminate any but the smallest quantities of sodium chlorid in the urine, may show no increase of the non-protein nitrogen in the blood. Indeed they may show an unusually good elimination of urea as measured by Ambard's constant and they may

excrete phenolsulphonephthalein even better than the average normal individual. On the other hand, patients with marked nitrogen retention may show little or even no albuminuria and they may exhibit no tendency toward edema or salt retention. The relation of nitrogenous retention to high blood pressure is also inconstant. Most patients with an increase of non-protein nitrogen in the blood show some increase in the systolic

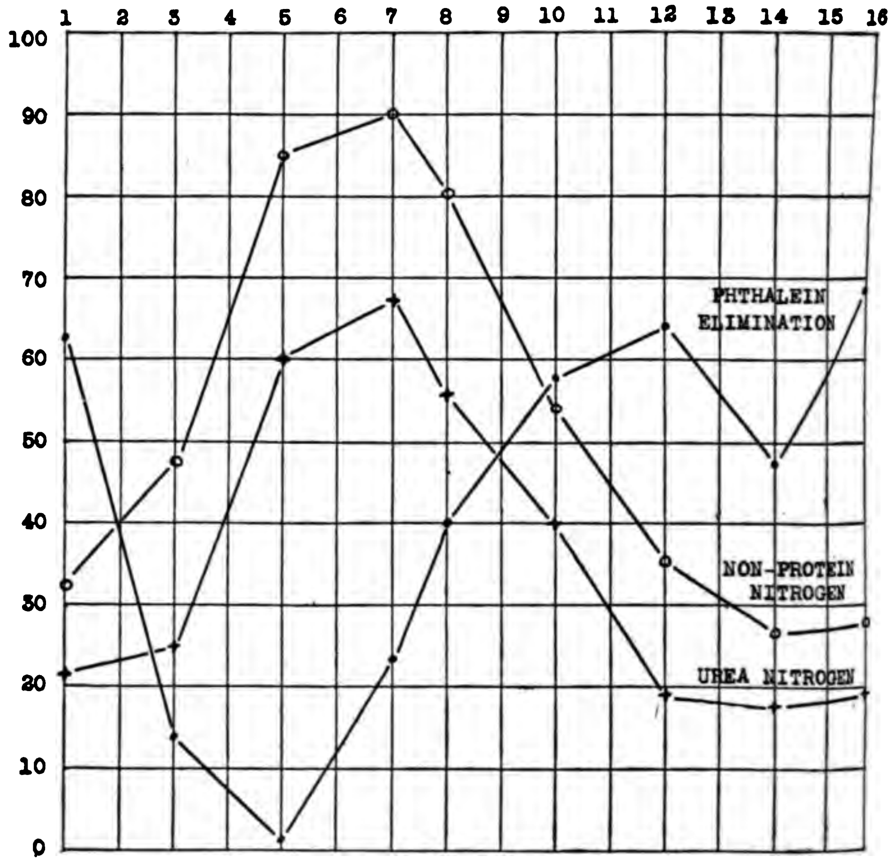

Fig. 94.—Diagram Showing the Excretion of Phenolsulphonephthalein and the Accumulation of Non-protein Nitrogen and of Urea Nitrogen in the Blood of a Rabbit During an Acute Nephritis Induced by Uranium Salts. Note that the Phthalein Excretion Changes More Promptly than the Accumulation of Nitrogenous Wastes. (Redrawn from Frothingham, Fitz, Folin and Denis, Arch. Int. Med.)

blood pressure; but high blood pressure is frequently present with no marked nitrogenous retention and in a given individual the variations in the non-protein nitrogen in the blood caused by changes in the diet are not necessarily associated with corresponding changes in the blood pressure. It is evident, therefore, that an increase in the non-protein nitrogen in the blood is not definitely related to the amount of albumin in the urine,

to the occurrence of edema, or to the height of the blood pressure. Patients with nephritis may, however, exhibit these manifestations in varying combinations.

Excretion of Dyes.—On the other hand, a general parallelism exists between an increase of non-protein nitrogen in the blood and the ability of the kidney to eliminate certain test dyes. Castaigne and Weill have made comparisons between the urea in the blood and the elimination of methylene blue and they have shown that a general but not a strict parallelism exists between the two. Similar results have been obtained in comparing the amount of non-protein nitrogen in the blood and the excretion of phenolsulphonephthalein. In the acute form of experimental uranium nephritis of rabbits, Frothingham, Fitz, Folin and Denis showed that the phthalein excretion falls rapidly and that with recovery it returns promptly to the normal. During the *first* stage the non-protein nitrogen accumulates in the blood and during the *second* it gradually returns to the normal level (Fig. 94). In experimental nephritis, therefore, the two tests give comparable results if one takes into consideration the fact that phthalein excretion indicates the renal function at the moment; whereas time enters as a factor in the accumulation and elimination of non-protein nitrogen. Studies on patients have also shown a general parallelism between the two tests. As a rule, a marked reduction in phthalein excretion is associated with nitrogenous retention. This parallelism is not an absolutely strict one. In chronic passive congestion particularly, there may be a marked reduction in the output of phenolsulphonephthalein with no corresponding accumulation of non-protein nitrogen in the blood.

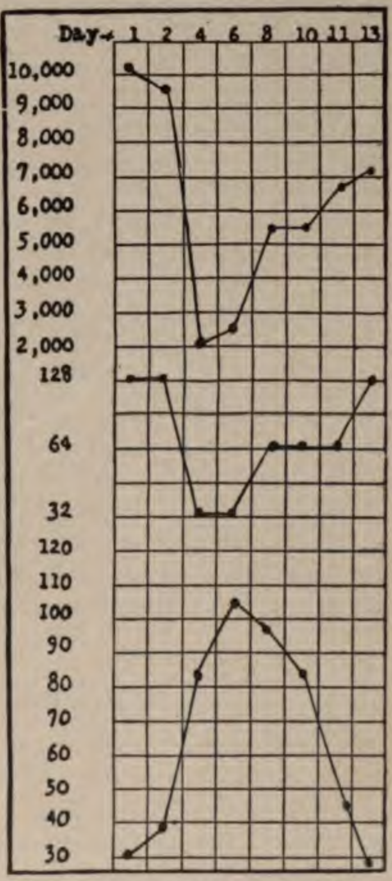

Fig. 95.—Curves Showing the Relation of Amylase Excretion (Upper Curve of "Absolute Diastatic" Strength, Middle of "d" Excretion) to the Accumulation of Non-protein Nitrogen in the Blood (Lower Curve) During a Moderate Nephritis Induced in the Rabbit by Uranium Nitrate. (From Fitz, Arch. Int. Med.)

Excretion of Amylase. — Wohlgemuth and a number of authors since him have shown that the amount of starch splitting ferment excreted in the urine of normal men is fairly constant and

that in nephritis the amount is frequently diminished in proportion to the severity of the disease. Geyelin compared the excretion of amylase with that of phenolsulphonephthalein and found that the two varied together in nephritis but that in cardiac insufficiency the phthalein was often reduced with no corresponding reduction of the amylase output. Fitz has compared the amylase excretion and the non-protein nitrogen of the blood in experimental uranium nephritis and has found that with the onset of the nephritis the excretion of amylase falls and the non-protein nitrogen of the blood begins to rise and that with recovery the reverse relationship occurs. (See Fig. 95.) It appears, therefore, that a diminished excretion of amylase occurs in those types of nephritis which lead to a retention of nitrogen.

Prognosis

Widal has pointed out that a marked increase in the non-protein nitrogen in the blood in chronic nephritis has an unfavorable prognostic significance and Rowntree and his associates have shown that a marked diminution in the excretion of phenolsulphonephthalein also indicates an unfavorable outcome. In judging prognosis from these tests, however, a number of modifying factors should be considered. It should be remembered that in acute nephritis and in the acute exacerbations of chronic nephritis these tests may be unfavorable and yet more or less complete recovery may take place. It should also be remembered that the amount of non-protein nitrogen in the blood is influenced by diet and that the phthalein test is influenced by the condition of the circulation through the kidneys. If, however, these modifying factors be taken into consideration, then these tests furnish important prognostic data in chronic nephritis; and their value is especially evident when we recall that serious accumulations of non-protein nitrogen may occur even when there is no edema and but little albumin in the urine.

Salt Retention—Nephritic Edema

Normal Relations

As a rule sodium chlorid is added to the food in order to improve its taste. The amount taken daily usually varies from seven to fifteen grams. Sodium chlorid leaves the body through various paths. Under ordinary circumstances the quantity excreted through the skin is very small and even after a sweat bath it rarely exceeds one or two grams. Small quantities are normally lost through the intestines and in pathological conditions this may be markedly increased. Most of the salt taken, however, leaves the body through the kidneys. When the intake of salt is constant, the amount excreted, though subject to consider-

able fluctuations, is on the whole equal to the intake. If an individual change from an ordinary diet containing from seven to fifteen grams of salt a day to one containing very small amounts (one to three grams), a new equilibrium is established. Before this occurs, however, the body usually loses a certain amount of salt which may amount in all to from five to fifteen grams. This loss of salt may be associated with little, if any, change in the body weight. It may, however, be accompanied by the loss of considerable water. In this way a fall of one to four pounds in the body weight may occur as the result of salt restriction. The rapid loss of weight during the first few days of complete starvation (page 222) has been attributed to a similar loss of salt and water from the body. If an individual who has been on a salt-poor diet returns to his original level of salt intake an equilibrium of salt intake and output again becomes established at the old level. Before this occurs, however, there is a retention of some salt in the body. This may or may not be accompanied by a corresponding retention of water. If water be retained, the weight increases to a corresponding degree. We see, therefore, that even in normal individuals a retention of salt is, at times, accompanied by a retention of water and a gain in weight. Under certain pathological conditions, this relation between salt and water retention becomes very striking.

Relation of Salt in Blood to Its Excretion.—We have seen that the excretion of urea depends upon its concentration in the blood and that according to Ambard the relation between the two can be expressed in mathematical terms, the urinary excretion at a given concentration being proportional to the square of the concentration in the blood. With respect to sodium chlorid the relations differ in that the concentration in the blood is more fixed and that when the concentration in the blood falls below a certain figure the excretion almost ceases. This threshold at which salt excretion practically ceases is fixed by Ambard and Weill at 5.62 grams per liter of blood for normal individuals. When the concentration of sodium chlorid in the blood rises above this figure its excretion in the urine, according to these authors, follows the same law for the excess above the threshold as is followed by urea for the total amount of urea in the blood; that is to say, the amount put out at a given urinary concentration is proportional to the square of the excess in the blood above the renal threshold and the amount put out at a given concentration in the blood varies inversely with its concentration in the urine.[1]

[1] FOOTNOTE:—The formula advanced by these authors would therefor be as follows:—

$$K = \sqrt{\frac{E}{D. \quad \sqrt{\frac{C}{14}}}}$$

Where E is the excess above the threshold in the blood; i. e., the amount of blood sodium chlorid minus its threshold value (normally 5.62 g. per liter), D is the total salt excretion calculated for 24 hours, and C is the concentration per liter in the urine. K should be constant for any given individual.

Sodium Chlorid as a Diuretic.—The administration of sodium chlorid to normal individuals, like the administration of other salts that can be absorbed by the intestinal mucous membrane, may, under certain circumstances, cause a diuresis which accompanies the excretion of the excess of salt given. The exact nature of the action of such salts upon the kidney is but imperfectly understood. It should be pointed out, however, that such diuresis is associated with changes in the composition of the blood. Following an intravenous injection of sodium chlorid or following its absorption from the intestinal tract the blood becomes more dilute by reason of a flow of lymph from the tissues into the blood. The hydremia that follows the ingestion of common salt is shown in the following experiments, taken from Benczúr. The percentage of protein in the blood was estimated by means of its refractive index (page 560):

Experiment II Aneurism of Aorta Received 12 g. NaCl at 8, fasting; drank nothing during experiment.			Experiment VIII Pulmonary Emphysema Received 12 g. NaCl at 8, 1½ hr. after breakfast; drank nothing during experiment.		
Time	Blood Serum		Time	Blood Serum	
	n_D	Percentage of Protein		n_D	Percentage of Protein
8.00	1,3500	8.2	8.00	1,3513	9.0
8.20	1,3504	8.5	8.20	1,3503	8.4
8.40	1,3504	8.5	8.40	1,3499	8.2
9.00	1,3492	7.8	9.00	1,3494	7.9
9.30	1,3495	7.9	9.30	1,3494	7.9
11.00	1,3496	8.0	11.00	1,3497	8.1
12.00	1,3496	8.0	12.00	1,3500	8.2
1.00	1,3497	8.1	1.00	1,3508	8.7

In certain forms of nephritis the retention of salt in the body may also be accompanied by an hydremia, but in this case the kidney fails to respond by excreting a larger quantity of urine.

Salt Retention in Nephritis

The ability of the diseased kidney to excrete sodium chlorid may be tested in various ways. In the first place, a single addition of salt may be made to the diet and the rapidity with which this excess is excreted may be estimated. In the second place, the ability of the individual to maintain a salt equilibrium at different levels of intake over more prolonged periods of time may be estimated. Finally, a comparison may be made

between the level of salt in the blood and its excretion in the urine and this may be compared with the normal relation by means of the mathematical formula devised by Ambard and Weill.

Excretion of a Single Addition of Salt.—We have seen that the addition of sodium chlorid to the diet of a normal individual results in an increased excretion, equilibrium being ultimately established at the new level of intake. When a single addition of salt to the diet is made,

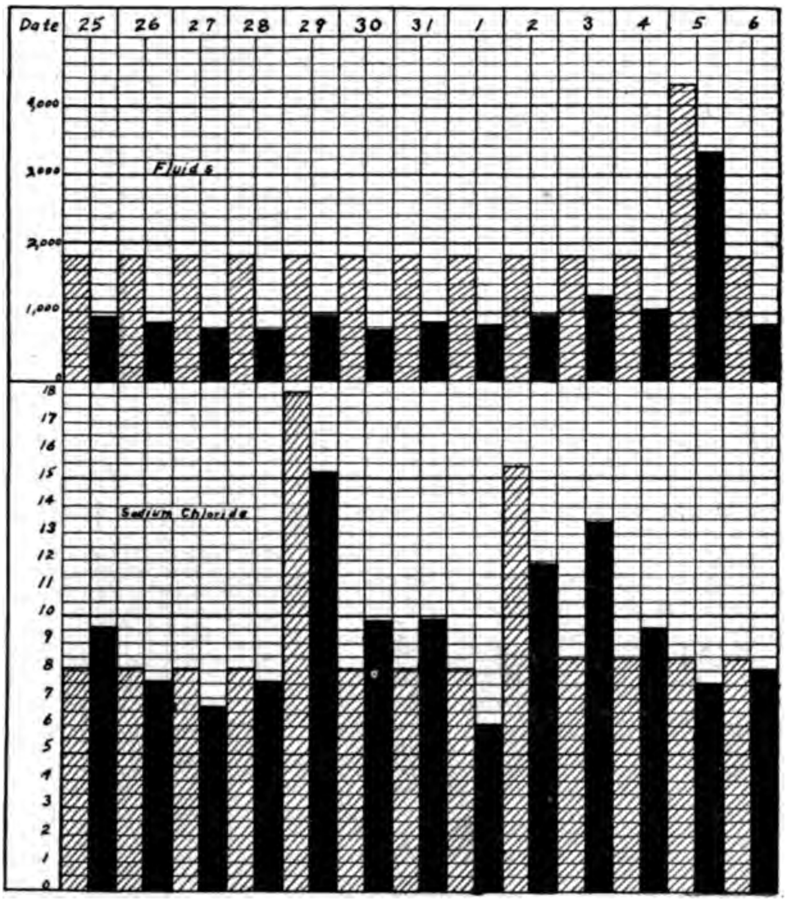

Fig. 96.—Normal Individual. Table Showing the Intake and Urinary Output of Water and Sodium Chlorid. The Intake Is Indicated by the Hatched Columns, the Output by the Solid Columns. Note that When Sodium Chlorid Was Added to the Diet, the Extra Amount Was Mostly Eliminated in One or Two Days with But Little Increase in the Diuresis. (Constructed from the data of Borelli and Girardi, Deutsch. Arch. f. klin. Med.)

the rapidity with which this excess is excreted varies according to circumstances. Under ordinary conditions of diet, the excess of salt is usually excreted within forty-eight hours (Fig. 96). If, however, the individual

has been on a restricted salt intake, the body seems to hold back the excess salt more tenaciously and several days may elapse before the excess is eliminated (Fig. 97).

Certain patients with nephritis show no deviation from the normal in their salt metabolism. In others, however, the single addition of an excess of salt to the diet may be almost without influence upon its excretion (Figs. 91 and 92). The retention of this excess of salt in the

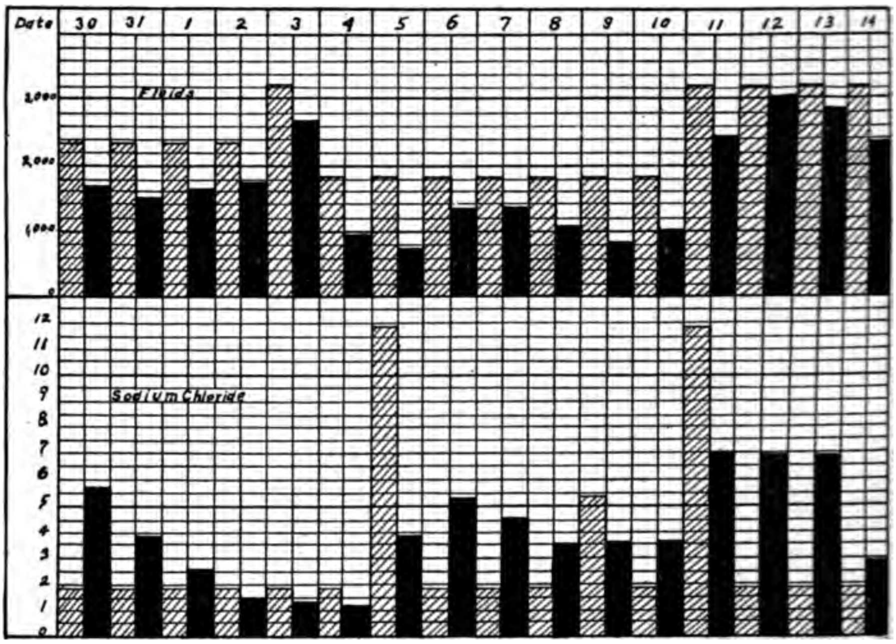

Fig. 97.—Normal Individual. Table Showing the Intake and Urinary Output of Water and Sodium Chlorid. The Intake Is Indicated by the Hatched Columns, the Output by the Solid Columns. Note that, When at the Start the Individual Was Placed on a Low Chlorid Intake, There Was a Progressive Loss of Sodium Chlorid from the Body, But that After About Three Days a Balance Became Established. When Sodium Chlorid Was Now Added to the Diet It Was Not Eliminated As Promptly As When the Individual Had Been on a Full Sodium Chlorid Intake. This Is Evident by Comparing with the Previous Figure from the Same Individual. Note Furthermore that in Both Figures the Water Output Followed the Intake Quite Promptly. In the Latter Figure the Elimination of Extra Sodium Chlorid Caused a Slight Diuresis. (Constructed from the data of Borelli and Girardi, Deutsch. Arch. f. klin. Med.)

body may or may not be accompanied by a retention of water and an increase in the body weight.

Continued Administration of Salt.—We have seen that the normal individual normally takes considerable salt in his diet and that he is able to establish an equilibrium between intake and output at widely different levels. Patients with nephritis vary greatly in their ability to establish such an equilibrium. While some can excrete the amount of salt taken in an ordinary diet, others may fail to do so. Their excretory ability may

be restricted to ten grams daily or in more serious cases it may be reduced even to one or two grams.

This ability to excrete salt also varies in the individual patient under varying circumstances. At times the addition of an excess of salt to the diet may result in a diminished output. The cause of this diminution is not understood. Possibly, as Widal suggests, it is due to an edema of the kidneys induced by the salt; possibly it exemplifies the general physiological law that when a function is overtaxed it is less efficient.

Edema from Salt Retention.—It has long been known that increases

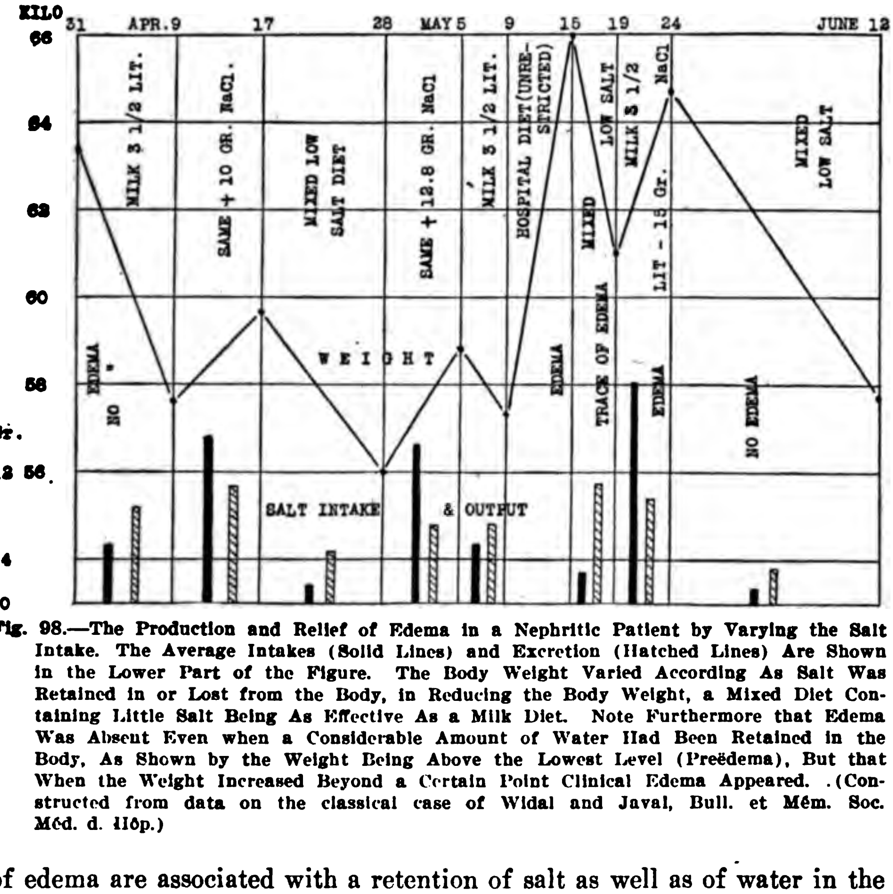

Fig. 98.—The Production and Relief of Edema in a Nephritic Patient by Varying the Salt Intake. The Average Intakes (Solid Lines) and Excretion (Hatched Lines) Are Shown in the Lower Part of the Figure. The Body Weight Varied According As Salt Was Retained in or Lost from the Body, in Reducing the Body Weight, a Mixed Diet Containing Little Salt Being As Effective As a Milk Diet. Note Furthermore that Edema Was Absent Even when a Considerable Amount of Water Had Been Retained in the Body, As Shown by the Weight Being Above the Lowest Level (Preëdema), But that When the Weight Increased Beyond a Certain Point Clinical Edema Appeared. (Constructed from data on the classical case of Widal and Javal, Bull. et Mém. Soc. Méd. d. Hôp.)

of edema are associated with a retention of salt as well as of water in the body, and that when edema disappears both salt and water are lost from the body. In some cases the retention of water may be primary and the retention of salt secondary, the latter being necessary in order to maintain a normal constitution of the body fluids. Sodium chlorid may, however, play a primary rôle in such combined retentions. Its great importance in nephritic edema was pointed out by Strauss in Germany and by Archard, Widal and their associates in France. In certain patients

with nephritis it has been demonstrated conclusively that it is possible to induce edema by giving large quantities of sodium chlorid and that it is possible to remove this edema by restricting the salt intake. This is well shown in Figure 98, which has been constructed from observations made by Widal and Javal on their classical case. It is evident that the weight of this individual could be varied at will by adding salt to or subtracting it from the diet.

Water retention in the body causes at first an increase in body weight with no demonstrable edema. During this period the appearance of the patient may not change, although in some cases the skin, especially about

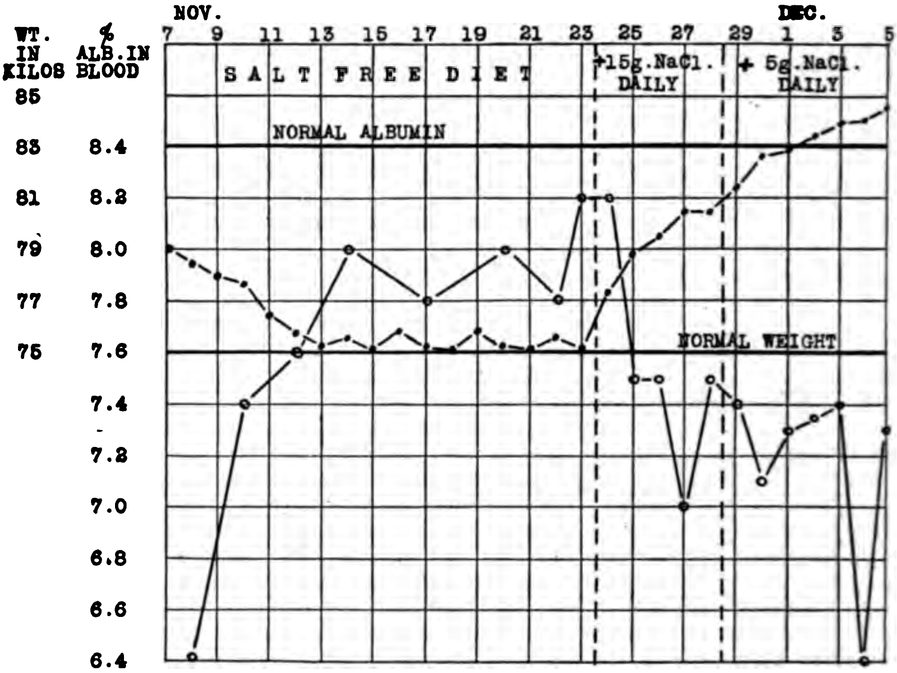

Fig. 99.—The Effect of Administration of Salt to a Nephritic Patient with Insufficient Salt Elimination. Note that During the Administration of a Diet Containing Little Salt the Body Weight Fell to a Fixed Level and the Concentration of Proteins in the Blood Increased. When Salt Was Added to the Diet the Weight Increased from Retention of Water and Hydremia Reappeared. (Drawn from Vaucher, Thèse de Paris.)

the face, appears smoother and fuller. Even at this early stage, however, there may also be a change in the concentration of the blood. The refractive index of the serum falls, which indicates a dilution of the blood with salt solution (Fig. 99). Clinical edema does not usually appear until the retained water has caused an increase of from ten to fifteen pounds in the body weight. There is, however, considerable individual variation in this respect, for in some patients edema does not appear until the weight has increased as much as twenty-four pounds.

Thirst.—It is possible by a rigid restriction of liquids to lessen the increase of weight which would otherwise occur from salt retention. Under such circumstances, however, the increased concentration of salt in the tissues causes an excessive thirst. If liquids are not restricted the individual drinks enough water to reduce the concentration of sodium chlorid in his body. Salt retention, therefore, acts partly by increasing the thirst. In this respect it differs from a retention of non-protein nitrogen. Urea and other nitrogenous waste products may accumulate in the blood without causing a retention of water, an hydremia, or an increased thirst. It is evident, therefore, that water retention does not depend upon a general increase in the molecular concentration of the body fluids but upon an accumulation of sodium chlorid or other salts in the body. The cause of this difference between sodium chlorid and urea seems to depend upon a difference in their diffusibility through animal membranes. Urea diffuses readily and its concentration in plasma and red corpuscles is approximately the same. Sodium chlorid and other salts do not diffuse readily and the salt composition of the plasma differs markedly from the salt composition of the red cells.

Differences Between Salt and Nitrogenous Retentions

The physiological differences between the retention of nitrogenous wastes and the retention of sodium chlorid are numerous. In retention of nitrogenous wastes their concentration in the blood and in the tissues is increased without necessarily causing a dilution of the blood (hydremia) or a retention of water within the body. As a result of the increase in the blood concentration the excretion of nitrogenous material through the kidneys is finally increased so that an equilibrium between nitrogenous intake and output is established. With sodium chlorid, on the other hand, retention tends to cause the retention of an equivalent amount of water. There results an hydremia and eventually an edema. The concentration of sodium chlorid in the blood plasma is but little affected. An increased administration of salt produces no corresponding increase in the elimination through the kidneys and there is, therefore, no tendency toward the establishment of a sodium chlorid balance between intake and output. The excessive salt is heaped up in the body in the edematous fluids.

Symptoms of Salt Retention

The symptoms which occur when marked chlorid retention is produced by giving excessive quantities of salt to nephritic patients have been studied particularly by Widal and his associates. In addition to the increase in weight, the hydremia and the edema of the subcutaneous issues there may be a variety of disturbances, many of which apparently depend upon edema of particular organs. Among these are râles and

edema of the lungs, headache, Cheyne-Stokes breathing and eclamptic attacks, vomiting and diarrhea, and finally an increase in the albuminuria.

Dry Retention

As a rule, any considerable retention of chlorids in the body is associated with a simultaneous retention of water which is shown by an increase of the body weight. Small fluctuations in the sodium chlorid balance may, however, occur without changes in body weight. A careful study of the intake and output of sodium chlorid over considerable periods of time has also shown that there may be a considerable retention of salt without the usual increase of weight from retention of water. This so-called dry form of sodium chlorid retention appears to be due to a deposition of sodium chlorid in the tissues. Studies on man as well as upon animals have shown that the percentage of salt in the tissues is not fixed and that it bears no constant relationship to the percentage of water present. Even though no edema be present, the organs of men may, under pathological conditions, show twice the normal amount of sodium chlorid and it is of particular interest that the skin often shows a relatively great increase in chlorids, even up to three times the normal (Leva).

Sodium Bicarbonate Edema

Water retention and edema have been produced in susceptible individuals by the continued administration of large doses of sodium bicarbonate. In practice this has happened most frequently when sodium bicarbonate was given to diabetic patients with acidosis for the purpose of warding off a possible coma. Sodium bicarbonate edema has also been produced in other patients, particularly when they already showed a tendency toward edema from any cause. In such cases there is not only a retention of water in the body but a retention of sodium and usually a retention of chlorids. Widal has maintained that in such cases the edema is due to the secondary retention of chlorids. F. Müller, on the other hand, expresses the opinion that in the edema produced by sodium bicarbonate as well as that produced by sodium chlorid, the sodium ion probably plays a more important part than the chlorin ion.

Primary Water Retention

Nephritic edema has been discussed thus far from the standpoint of sodium chlorid retention and this has been done because of the remarkable variations in edema which have followed variations in the sodium chlorid intake of certain nephritic patients. From the practical standpoint this intimate relationship between nephritic edema and the intake of sodium chlorid is of great importance. It seems probable, however, that edema may also occur from a primary water retention accompanied by a second-

ary retention of sodium chlorid. In acute nephritis, for example, with more or less suppression of the urine there may be a primary water retention. In chronic nephritis, also, the elimination of water ingested may not be so complete or so prompt as in health. There is reason to believe, therefore, that a primary water retention may occur in nephritis. Whether or not this is a frequent cause of nephritic edema we do not know. As a rule, the edema of chronic nephritis without cardiac insufficiency is associated with a deficient capacity for sodium chlorid elimination by the kidneys.

Renal and Extrarenal Factors

Renal Factors in the Production of Edema.—Thus far we have spoken of a retention of sodium chlorid and of water in the bodies of nephritic patients. The mechanism of this retention is not well understood. Possibly it is due to an insufficient activity of the kidneys; but it may also be due to changes in the blood, the blood vessels or the tissues, of such a character that salt or water or both are held in the body and do not reach the kidneys in proper quantity or in a proper physical or chemical state for excretion. The marked hydremia which always accompanies nephritic edema shows that the blood contains a larger percentage of water than normally. The inability of the diseased kidney to eliminate water is therefore not due to any increased concentration in the blood that is supplied to it.

Nor is the defective elimination of salt due to a lack of salt in the blood. We shall point out later (page 478) that the failure to excrete chlorids in pneumonia may be attributed to such a lack of sodium chlorid in the blood. In nephritis with salt retention, however, the percentage of salt in the blood is normal or increased and the amount of sodium chlorid excreted in the urine is not so great as one finds in a normal individual with a similar percentage of salt in the blood. McLean has calculated from the Ambard formula the quantity of sodium chlorid in the blood which would correspond to the amount eliminated in the urine and finds that in chronic nephritis the blood contains larger quantities of sodium chlorid than one would expect normally (Fig. 100). It is evident, therefore, that the failure to eliminate chlorids like the failure to eliminate water cannot be attributed to their deficient concentration in the blood, and it seems probable, therefore, that the defect lies in the kidneys themselves.

Extra Renal Factors.—Considerable evidence has been advanced to show that the blood vessels of the body play an important part in the etiology of nephritic edema. In patients, as we have seen, the amount of water which must be retained in the body in order to produce edema is variable. In animal experiments it has been noted repeatedly that the degree of edema and its localization vary, even though the same amount of

water is retained in the body. Indeed, subcutaneous edema does not occur even when large quantities of salt solution are transfused rapidly into normal animals. Furthermore, experimental edema is more readily produced when vascular poisons, such as arsenic or snake venom, are used in addition to the poisons which damage the kidney tubules. Whether these vascular poisons increase the tendency toward edema through their action upon the renal vessels or through their action upon the vessels in other parts of the body, is not certain.

The vascular permeability of nephritic animals has been tested by determining the rapidity with which various solutions leave the blood vessels after their intravenous injection. In order to eliminate the action of the kidneys in such experiments the latter have been thrown out of function either by ligation of the ureters or by double nephrectomy. The results of such experiments have not been uniform. Schmid and Schlayer found that the vessels of animals previously injected with large doses of the vascular poisons were unusually permeable to sodium chlorid solutions. Boycott and Chisolm, on the other hand, found that in experimental uranium and chromate nephritis the body vessels were less perme-

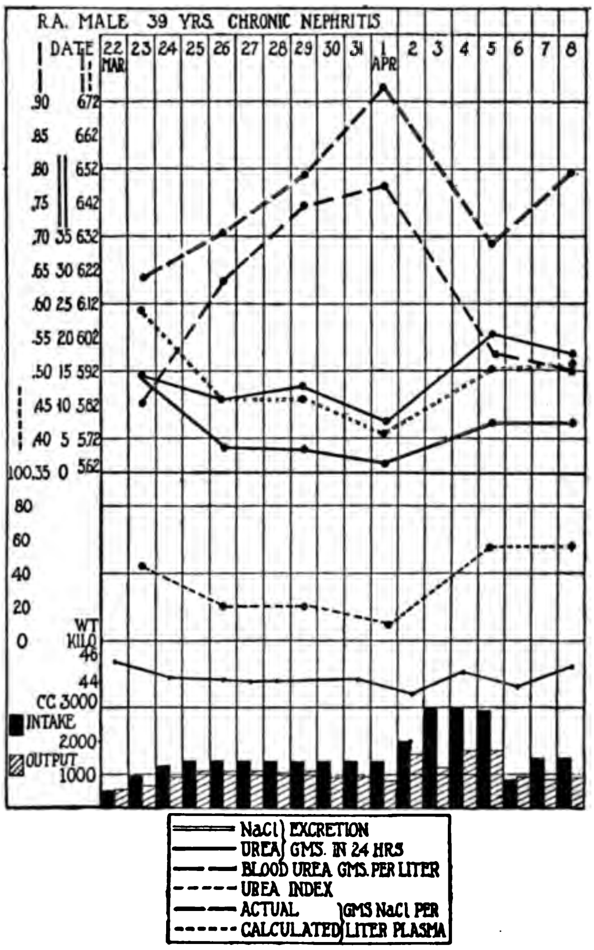

Fig. 100.—The Relation Between the Level of Sodium Chlorid in the Blood of a Nephritic Patient and the "Calculated" Level that Would Be Expected in a Normal Individual Who Was Excreting the Same Quantity of Salt in the Urine. Note that in This Patient the Level in the Blood Was Higher Than One Would Expect For a Normal Individual. From March 23 to April 2 the Fluids Were Restricted and Salt and Food Were Allowed ad libitum. After April 2 the Fluids Were Increased and the Food and Salt Restricted. (From McLean, Jour. Exp. Med.)

able to salt solution, to gelatin solutions, and to protein solutions. We see, therefore, that while general considerations suggest that an unusual permeability of the blood vessels plays a part in the occurrence and localization of nephritic edema, the exact rôle of the blood vessels has not been definitely established.

It has also been suggested that nephritic edema may be due to a change in the chemical or physical character of the tissues themselves of such a character that these attract and hold salt or water or both. The deposition of salt particularly in the skin favors this view. Many localized edemas are doubtlessly due to local changes in the blood vessels or tissues, as is the case, for example, in inflammatory edema. In nephritic edema, however, the water is not intimately bound to the tissue substance. It readily redistributes itself about the body under the influence of gravity or pressure. Furthermore, when openings are made into the subcutaneous tissue the liquid runs out freely. It would seem, therefore, that in nephritic edema an excessive amount of free liquid is retained in the body. Definite evidence that it is fixed in nephritic tissues has not been furnished.

Relation of Edema to Other Nephritic Manifestations

No fixed relation exists between salt and water retention and the other manifestations of nephritis. Edema may be marked without any coincident retention of urea or non-protein nitrogen and a marked retention of waste nitrogen may be present when the excretion of chlorids and of water is normal. As a rule, patients with nephritic edema have considerable albumin and numerous casts in the urine. On the other hand, a few very remarkable cases have been reported (Wyss, Palmer) in which an edema was relieved by a restriction of salt intake, although no albumin was present in the urine. The relation of such cases to disease of the kidneys remains to be established.

Acidosis and Renal Disease

In addition to the removal of nitrogenous wastes and the preservation of a normal water and salt concentration in the body, the kidney performs an important function in regulating the chemical reaction of the body. During catabolism various acid bodies are formed. The most important of these are carbonic acid from the oxidation of carbon containing compounds, and sulphuric and phosphoric acids from the oxidation of substances containing sulphur and phosphorus in organic combinations. Organic acids are also formed, particularly under pathological conditions. In spite of this constant formation of acid substances the chemical reaction of the body fluids remains practically neutral. This neutral reaction

is maintained, first, by neutralizing some of the acids with ammonia derived from organic compounds and, second, by the elimination of acid substances from the body (see Acidosis). Carbon dioxid is given off in the lungs, and the kidneys secrete an acid urine.

Occurrence.—It might, therefore, be expected that diseases of the kidneys may lead to an imperfect regulation of the acid content of the body and to an accumulation of acid products. Examinations have shown that in nephritis the tension of carbon dioxid in the alveolar air is frequently diminished, which is, as we have seen, an evidence of acidosis. Milder grades of acidosis in certain patients with kidney disease may also be demonstrated by the fact that unusual quantities of sodium bicarbonate are required in order to render the urine alkaline to litmus, and also by the fact that a given quantity of sodium bicarbonate may fail to cause the usual reduction in the acidity of the urine. According to Sellards, definite changes in the titratable alkalinity of the blood can be demonstrated in certain diseases of the kidney. The curve of hemoglobin dissociation (page 362) may also indicate a collection of acid in the blood. It is evident, therefore, that an acidosis can be demonstrated in some nephritic patients.

Cause.—The cause of the acidosis of kidney disease is not well understood. That it may be due in part to an increased formation of acids in the body cannot be denied and indeed it seems quite possible that this may play a part in its etiology. On the other hand, this can hardly be the sole cause of the acidosis, for the normal kidney can when necessary excrete much larger quantities of acid than are excreted in cases of nephritis. Furthermore, when the urine has once been rendered alkaline the signs of acidosis do not return promptly, as is the case when the acidosis is due to the formation of large quantities of acid in the body (diabetes). It would appear, therefore, that the acidosis present in these patients is due mainly to an imperfect control of the body reaction by the kidneys.

Symptoms of Acidosis.—To what degree the acidosis that has been demonstrated in certain patients with nephritis is responsible for the symptoms present is still undetermined. Lewis and his coworkers believed that acidosis is responsible for the dyspnea so commonly present in cardiorenal disease. We have already pointed out (page 374) that it is not possible to account for all types of cardiorenal dyspnea on this hypothesis. Nevertheless, it occasionally happens that the acidosis in advanced renal disease is so marked that it may well be responsible for the dyspnea present and in certain patients the administration of sodium bicarbonate in large doses has relieved the dyspnea (Sellards, Peabody).

As a general rule, the acidosis of renal disease runs parallel to the accumulation of waste nitrogen in the blood and to the ability of the individual to eliminate phenolsulphonephthalein (Peabody). In uremia of this type the dyspnea is often marked and is due in part to an acidosis. To

what extent the other manifestations of uremia are due to this cause will be discussed in the paragraphs on Uremia.

Acidosis and Edema.—Martin H. Fisher has attributed to acidosis a preponderating rôle in the etiology of nephritic albuminuria and edema. His theory is founded mainly upon the experiment that fibrin swells when placed in acid solution. It has been shown, however, by Henderson and his associates that the concentrations of acid used in Fisher's experiments were far in excess of any known to occur within the body. Clinically no definite relation seems to exist between the degree of edema and the degree of acidosis as measured by the usual methods. Patients have been observed in whom there was marked edema without evidence of acidosis, while other patients and particularly diabetics have shown marked acidosis but no edema. There is no convincing evidence that acidosis is a cause of edema in patients with nephritis.

The Administration of Alkalis in Nephritis.—The hypothesis that acidosis causes renal disease or certain of its manifestations is of great importance for the reason that acidosis may be combatted by the administration of alkalis such as sodium bicarbonate. In recent years alkalis have frequently been given to nephritic patients. The results have been rather inconstant and the time is not yet ripe for a final opinion as to their value and the manner in which they act. In certain instances nephritic patients showing marked acidosis have been relieved of toxic or dyspneic symptoms by the administration of sodium bicarbonate. In others edema has improved or disappeared. It should be remembered, however, that edema has also been produced or increased by the administration of sodium bicarbonate. In still other cases the amount of albumin in the urine has been reduced by the administration of sodium bicarbonate. Here again, however, the effects seem to be inconstant; for while in some patients the albumin has diminished, in others it has not been affected and in still others albuminuria has been produced or increased by the administration of large quantities of sodium bicarbonate.

Renal Function in Heart Disease

Cardiac disturbances are common in diseases of the kidney; and conversely the functions of the kidney may be altered as a result of chronic passive congestion attendant upon cardiac failure. It is indeed frequently difficult to determine the relative parts played by chronic renal congestion on the one hand, and by primary disease of the kidneys on the other, in the production of a given renal complex.

Experimental Congestion.—Experimentally it has been shown that in moderate degrees of renal passive congestion the excretion of sodium chlorid, potassium iodid, and lactose may be interfered with. With a

more severe congestion there is a diminished elimination of phenolsulphonephthalein.

Elimination of Water and of Sodium Chlorid.—Studies on patients with moderate grades of cardiac decompensation have shown that when unusual quantities of water or of salt are added to the diet these are eliminated in some cases in a normal manner. Other patients and particularly those with edema and with marked oliguria fail to eliminate extra quantities of water or of salt taken during the day. During the oliguria from congestion, there is not only a decrease in the total quantity of sodium chlorid eliminated but its concentration in the urine may also be low. In patients with heart disease the administration of large quantities of sodium chlorid may increase the edema on account of the insufficient elimination of this salt through the kidneys. When the circulation improves and diuresis occurs, large quantities of sodium chlorid that have been retained in the body are eliminated.

Nitrogen Excretion.—In contrast to the frequent and severe disturbances of salt and water elimination during broken compensation, the excretion of nitrogenous waste products is usually but little affected. This has been demonstrated not only by giving to such patients large quantities of urea and determining the rate at which it is eliminated but also by examining the blood for non-protein nitrogen and for urea. Even when very small quantities of urine are being passed the congested kidney ordinarily responds to the administration of an additional amount of urea by excreting it in unusual concentration. Only in rare cases with marked oliguria is the nitrogenous elimination imperfect and only in such cases is there a definite accumulation of non-protein nitrogen in the blood.

Functional Tests.—The elimination of lactose is nearly always markedly reduced in cases of passive congestion and the elimination of potassium iodid is also frequently delayed. The phenolsulphonephthalein output is often reduced in marked congestion. It is in such cases particularly that a discrepancy occurs between this test and the accumulation of waste nitrogen in the blood. In chronic passive congestion of the kidneys the phthalein elimination may be markedly reduced without any considerable increase in the incoagulable nitrogen of the blood.

Renal Function in Eclampsia

The kidney changes in eclampsia are no longer regarded as the sole cause of this symptom complex. Nevertheless considerable interest is attached to the study by modern methods of the renal function in cases of threatened and of fully developed eclampsia. Although the urine may be considerably reduced in amount the percentage of nitrogenous material therein is often high and the total elimination is usually good. The non-

protein nitrogen of the blood, though usually somewhat increased in eclampsia, rarely reaches the high level of what would be regarded as a serious nitrogenous retention in chronic nephritis. Similarly, although the output of phenolsulphonephthalein is frequently reduced in eclampsia, this reduction does not parallel the severity of the symptoms and it may be insignificant when the symptoms are marked. It is evident, therefore, that the symptoms of eclampsia do not depend upon an insufficient elimination of urea or of the total nitrogenous waste products from the body.

Patients with eclampsia frequently show marked edema with chlorid retention and when the edema disappears large amounts of sodium chlorid are excreted in the urine. Whether this retention of chlorids bears any relation to eclamptic manifestations other than the edema is not known. Zinsser believes that a marked fall in the output of chlorids has an unfavorable prognostic significance. It is possible, however, that other unknown substances are retained with the chlorids and that these rather than the chlorids are responsible for some of the toxic symptoms of eclampsia.

Uremia

Patients with nephritis not infrequently show a variety of disturbances which appear to be of a toxic character and which not infrequently prove fatal. To these the name of uremia has been given. It is unnecessary to review the numerous theories which have been advanced to explain these toxic symptoms in nephritis. Some symptoms often regarded as toxic are doubtlessly due to circulatory disturbances dependent upon an associated cerebral arteriosclerosis and they are, therefore, not of a direct toxic character. If these be omitted from consideration the toxic theories of uremia may be grouped in two general classes. According to the *first* of these, uremia results from a retention in the body of substances which should be eliminated in the urine. According to the *second* group of theories, the manifestations of uremia are due not to the retention of substances formed in normal metabolism but to abnormal toxic substances formed as a result of a perverted metabolism during kidney disease.

It seems certain that the toxic symptoms in nephritis are not all due to a single cause and that consequently the term uremia, as commonly used, embraces a number of distinct conditions. Studies of the non-protein nitrogen in the blood have enabled us to separate two general groups of such toxic conditions. On the one side are those cases in which there is a marked increase of non-protein nitrogen and of urea in the blood. On the other side are the cases in which such an increase, if present, seems insufficient to account for the symptoms. Each type presents more or less characteristic symptoms, and each will be discussed separately.

Uremia with Marked Nitrogenous Retention

The toxic symptoms which occur in patients who show unusually large quantities of non-protein nitrogen in the blood have already been described in discussing nitrogenous retention. It will be recalled that slight or moderate degrees of retention are not associated with characteristic clinical symptoms. As the retention increases, however, the patient develops a condition of bodily weakness and mental apathy. He becomes drowsy, but as a rule can be aroused without great difficulty. Headache, dizziness and loss of appetite are common. Vomiting or diarrhea may occur. Itching is said to be a characteristic manifestation of this type of uremia. The blood pressure which at the onset is usually elevated may go still higher; but in long-continued cases with progressive weakness it tends eventually to fall to a lower level. Marked anemia of a secondary type is common. Gradually such patients become more prostrated and more apathetic. Death may occur quite suddenly, suggesting a cardiac death. More rarely the patient becomes comatose shortly before death. In this type of renal intoxication there may be muscular twitchings; but general convulsions, paralysis and other serious or localized nervous manifestations are frequently absent.

Pathogenesis.—The exact cause of the symptoms is uncertain. The degree of nitrogenous retention and the severity of the symptoms do not run exactly parallel. Before death the non-protein nitrogen in the blood usually exceeds 150 mgm. per 100 c.c. of blood, but much higher figures (300 mgm. and more) have been observed. That the symptoms depend in part upon the concentration of the retained substances in the body seems probable from the fact that a number of cases have been recorded in which marked diuresis has precipitated an attack of uremia in nephritic patients. In such cases the sudden loss of water from the body has evidently led to uremia through an increased concentration of the toxic substances.

A marked increase of the non-protein nitrogen in the blood is due in the main to an accumulation of urea. Urea is not ordinarily regarded as a toxic substance, yet it is possible that in the concentrations found in the blood of these patients it may be responsible for at least some of the symptoms. Recent experiments conducted with Gilbert and Wickett indicate that as a result of the ingestion of 100 grams of urea by normal individuals the urea nitrogen of the blood can be raised to 100 mgm. per 100 c.c. or more, figures which are not infrequently obtained or exceeded during the nitrogenous retention of chronic nephritis. When the blood urea exceeded 70 mgm. of urea nitrogen, symptoms of headache, dizziness and slight somnolence occurred. Whether these were due to the sudden alteration in the composition of the body tissues and fluids or whether they were toxic effects produced by the urea itself or the alteration in the molec-

ular concentration of the body fluids has not been determined, but such symptoms suggest that urea in the concentration ordinarily found in this type of uremia may be directly responsible for some of the symptoms observed.

It should be remembered, however, that the type of uremia which we are now considering is also characterized by an increased concentration of other nitrogenous bodies in the blood, among which are creatin, creatinin,

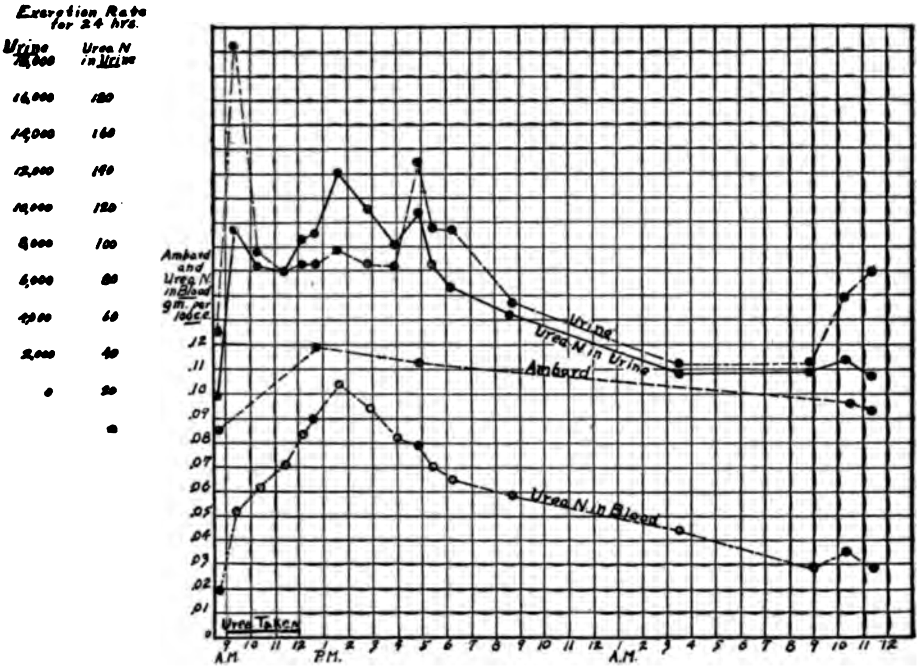

Fig. 101.—Effect of Ingestion of Large Quantities of Urea Upon a Normal Individual. Between 9 A.M. and 12 M. 100 Grams of Urea Were Taken. The Amount of Urea Nitrogen in the Blood Rose to Over 100 mgm. per 100 c.c. From 10:30 A.M. to 5:30 P.M. the Subject of the Experiment Complained of Headache, Dizziness and Some Stupor. (From unpublished experiments by Hewlett, Gilbert and Wickett.)

uric acid and indican. While the toxic effects of comparable accumulations of these substances have not been demonstrated, nevertheless it is possible that they may exert some poisonous effect. Possibly also other substances of a more complex and toxic nature are retained in the body and are present in the undetermined fraction of non-protein nitrogen in the blood. The latter is often increased in uremic patients (page 424).

Finally, this type of uremia is usually accompanied by a more or less marked acidosis. That this acidosis may in certain cases produce dyspnea has already been noted and the dyspnea of this origin may improve if sufficient alkali be given to render the urine alkaline. The failure of the alkaline treatment to relieve uremic symptoms in all cases and the persistence of toxic symptoms even after the signs of acidosis have disappeared

indicate, however, that acidosis cannot be the sole cause of the uremic complex.

Uremia Without Marked Nitrogenous Retention

As opposed to the above type of uremia, which develops in patients who show unusual quantities of non-protein nitrogen in the blood, we have one or more other types in which there is either no such increase or in which the increase, though present, seems insufficient to explain the clinical symptoms. To this group belong the cases which show uremic convulsions. In these as well as in the convulsive type of eclampsia there is no necessary increase of the non-protein nitrogen in the blood, and the elimination of phenolsulphonephthalein may be normal or only moderately diminished. At the present time we are quite ignorant as to the immediate cause of the symptoms in such cases. Presumably they are due to the action of some unusually toxic substance which may be retained in the body owing to a specific impermeability of the kidney or which may be formed owing to some associated disturbance in the general or local (i. e., renal) metabolism. Of unusual interest in this connection is the observation of N. B. Foster, who succeeded in isolating from the blood of patients with epileptiform uremia a toxic substance which caused the death of small animals on injection.

Numerically these uremias are more rare than those with considerable retentions of nitrogenous wastes. The clinical picture is so striking, however, that convulsions are always mentioned in descriptions of uremia. Other severe central nervous manifestations, such as psychoses and paralyses, may also occur with no considerable increase of the non-protein nitrogen in the blood. In at least some of these cases, however, the symptoms are due to an associated cerebral arteriosclerosis.

Renal Calculi

Solution of Salts in the Urine

The urine holds a considerable variety of salts in solution. The laws which govern this solution and the conditions which lead to a precipitation of the salts are, however, but imperfectly understood. The precipitation of solids depends only in part upon their concentration in the urine, for numerous observations have shown that the amounts and characters of urinary sediments bear no definite relationship to the concentration of these various substances in the urine. The formation of sediments is markedly influenced by the reaction of the urine. Certain constituents, like uric acid and the urates, are more apt to be precipitated from acid urine; while others, like calcium phosphate and oxalate, are more apt to be precipitated from alkaline urine.

High Saturation.—It should be noted that many salts are present in

the urine in a concentration far greater than can be attained in a simple aqueous solution of these same salts. This is true of uric acid, the urates, and calcium oxalate. Nor is this high concentration in the urine a simple supersaturation. When crystals of a salt are added to a supersaturated solution, the excess of the salt is rapidly precipitated. If, on the other hand, a crystal of uric acid be added to urine, the precipitation of uric acid takes place slowly and less completely than if the crystal were added to a supersaturated solution of uric acid in water. Even after many hours the amount of uric acid still dissolved in the urine may be several times the amount that pure water will hold in solution.

Colloids.—Apparently, therefore, many salts of the urine are held in solution by other urinary constituents. According to Lichtwitz, colloidal substances play the most important rôle in maintaining this solution. When urinary salts are separated from these colloidal substances by dialysis, and the dialyzate is concentrated to the original volume of the urine used, a sediment of uric acid, calcium oxalate, and calcium phosphate is formed. Clear alkaline urines become cloudy only after hours, whereas if shaken with ether so as to remove the colloids soluble in ether a precipitation of phosphates may occur immediately. Changes in the urinary colloid may also account for the fact that a variety of salts are frequently precipitated at one time, as well as for the observation that a patient who at one time shows numerous calcium oxalate crystals in the fresh urine, may at another time show only phosphate precipitates.

Composition of Calculi

Inorganic Salts.—Calculi found in the pelvis of the kidney are usually composed chiefly of calcium oxalate. Less commonly such stones are made up of uric acid, urates, cystin, xanthin, etc. In the bladder, where alkaline decomposition of the urine frequently follows an obstruction of the lower urinary tract, stones containing considerable calcium carbonate and basic phosphates are common, for these salts are readily precipitated from an alkaline urine. If the bladder urine remains acid, uric acid stones may occur.

Protein Framework.—In addition to these crystalline substances, all urinary calculi contain a framework composed of protein matter. If the mineral portion of a stone be dissolved, this organic residue can be stained with eosin, and it is seen to extend through all portions of the stone.

Nucleus.—The nucleus of a urinary calculus may be composed of foreign matter. Various foreign substances, when introduced and left in the bladder, have become centers of stone formation. In the center of the stone may also be found parasites such as the Bilharzia or clumps of bacteria. Again, an old blood clot or a remnant of tissue has been found. More commonly, however, the nucleus of the stone contains no such for-

eign material, but appears, like the stone itself, to be formed by a precipitate composed of mineral and colloidal elements. The development of a calculus about such a center is greatly favored by urinary stasis, for it is evident that under ordinary circumstances nuclei, while still small, will be readily evacuated in the urine, and no opportunity is given for the gradual growth of a calculus.

Growth.—Calculi grow by the deposition of layers to the exterior. From what has been said regarding the important part played by colloids in holding the urinary salts in solution, it seems probable that these depositions on the nucleus or on the growing stone are intimately associated with changes in the colloidal chemistry of the urine. The protein framework is made up of such colloidal substances, and their deposition may cause secondary changes in the solubility of the organic substances in the immediate neighborhood. The exact mechanism, however, is not clear.

Urinary calculi usually show a concentric laminated structure, which indicates that depositions have taken place in varying amounts and at varying rates during the growth of the stone. Not infrequently these laminae also show variations in chemical composition, different salts being precipitated at different periods. These variations in the composition of the successive laminae depend in part upon variations in the composition of the urine as well as upon variations in its chemical reaction. Intercurrent or varying degrees of infection may also cause changes in the reaction of the urine. Furthermore, they change its colloidal composition by the admixture of mucinous material, bacteria and pus. Although infection plays an important part in the formation and growth of many calculi, it does not seem to be essential for stone formation.

Hydronephrosis

The older experiments of Cohnheim, Albarran and others have shown that a sudden and complete obstruction of the ureter does not lead to a marked degree of hydronephrosis. As a result of such an obstruction, there is an acute rise of pressure in the pelvis of the kidney which may reach 73 mm. of mercury within an hour. The kidney becomes congested and hemorrhages may occur into the renal substance and into the cavity of its pelvis. On account of the high pressure and the renal changes the secretion of urine soon ceases, and if the obstruction continues there is eventually an atrophy of the kidney, with a partial or complete absorption of the fluid present in the pelvis. No marked hydronephrosis occurs.

Experimental Production

Hydronephrosis has been produced experimentally by causing partial or intermittent closure of the ureter. This has been accomplished in some

cases by moderate constriction from without, produced by ligatures or scar tissue following the injection of irritating substances. Partial obstructions from calculi which were produced experimentally by feeding oxamid to rabbits have also led to hydronephrosis. Finally, hydronephrosis has been produced experimentally by loosening the attachments of the kidney while the ureter was kept fixed, thus causing an intermittent closure of the ureter by kinking.

Etiology in Man

Congenital.—In man hydronephrosis may be due to congenital or acquired causes. In the development of the ureter it passes through various stages during which constrictions and folds are apt to occur, particularly at its junction with the pelvis of the kidney and also near the bladder. Normally these disappear in the later stages of intra-uterine life owing to the growth of the embryo and the secretion of urine. In some, however, these congenital abnormalities persist. Even in intra-uterine life they may lead to the formation of hydronephrosis. More commonly, however, the disease does not become evident before the second or third decade. Examination may then show valvelike structures due to folds at the beginning of the ureter or less commonly there may be a partial obliteration of the lumen. Among other congenital causes for hydronephrosis are unusual positions of the kidney with irregularities in the insertion of the ureter.

Anomalous renal blood vessels lying close to the upper end of the ureter have been noted repeatedly in cases of hydronephrosis. Fenwick estimated that these were present in 16 per cent of all cases of hydronephrosis. They were found in twenty of twenty-seven cases reported from the Mayo clinic. The frequency with which these have been described and the fact that in some cases at least the hydronephrotic dilatation extended to, but not below, the anomalous blood vessel makes it probable that such vessels may play an important rôle in the etiology of certain cases of hydronephrosis (Fig. 102).

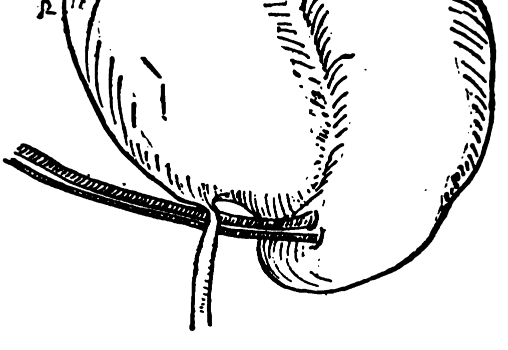

Fig. 102.—Hydronephrosis with Compression of the Ureter by Aberrant Renal Vessels. Sketch Made During an Operation. (From Mayo, Brasch, and MacCarty, Jour. Am. Med. Assn.)

Acquired.—Hydronephrosis is usually acquired as a result of a partial obstruction to the outflow of urine. This may be due to the presence of calculi in the pelvis of the kidney or in the bladder, it may be due to the pressure of a tumor on a ureter, or it may be due to a urethral obstruction from an enlarged prostate or a stricture.

The relation between movable kidney and hydronephrosis is an interesting one. It is evident that when a kidney is displaced, kinking or compression of the ureters may cause partial or temporary obstructions to the outflow of urine. Furthermore, hydronephrosis has been produced experimentally by loosening the renal attachments. Clinically slight or moderate dilatations of the renal pelvis are not uncommon in patients with movable kidneys. Marked degrees of hydronephrosis, however, are rather unusual in this class of patients.

Symptoms

The symptoms of hydronephrosis are surprisingly few so long as the fluid accumulates gradually. Sudden retentions, however, cause severe symptoms. Not uncommonly, therefore, the symptomatic manifestations of hydronephrosis are of an intermittent paroxysmal character. During a paroxysm there is severe pain on the affected side, which may be accompanied by a diminished flow of urine and the appearance of a palpable tumor in the lumbar region, evidently due to a rapid accumulation of fluid in the hydronephrotic sac. Following the paroxysm there is frequently a profuse flow of urine which may even be greater than the estimated contents of the hydronephrotic sac. Such paroxysms seem to be caused by sudden closure of the upper end of the ureter by kinks or by valves which lead to an acute retention of fluid in the pelvis of the kidney. The unusual flow of urine which follows the paroxysms is due, not only to a discharge of the collected fluid, but also to an unusual secretion of urine by the partly damaged kidney. Where a tumor appears during the attack of pain the relation between the paroxysm and the intermittent hydronephrosis is an evident one. In certain patients with movable kidney similar attacks also occur (Dietl's crisis). Although there may be no palpable enlargement of the kidney, the capacity of the renal pelvis as determined by the injection of fluid through the catheterized ureter is nearly always increased in such patients (Hunner). It is probable, therefore, that Dietl's crises are really manifestations of an intermittent collection of urine in the pelvis of the kidney.

Renal Pain

Pain is not a constant or characteristic symptom of nephritis. Some patients complain of backache and occasionally the pain is quite severe. Such severe pain is usually assumed to be due to an acute distention or

inflammation of the renal capsule, to acute renal congestion, to infarcts, etc.

Typical renal colic, with violent paroxysms of pain, nausea, and vomiting, usually occurs only in diseases affecting the renal pelvis or the ureter. Such pains have been attributed either to lesions of the lining mucous membrane or to increased tension or spasm of the smooth muscle. It is doubtful if severe pain is ever caused by injuries or lacerations of the mucous membrane. We know that pyelitis may cause no pain and that large calculi may remain in the pelvis of the kidney for years without pronounced symptoms. On the other hand, there is positive evidence that an acute obstruction to the outflow of urine through a ureter will cause the typical pain of renal colic. Colic in man has followed an accidental but complete obstruction of a ureter during an operation. Furthermore, Kelly has shown that when a ureter is catheterized and fluid is injected into the pelvis of the kidney in order to determine its capacity, typical attacks of renal colic may be produced by the overrapid injection of large quantities of fluid. It is evident, therefore, that an acute distention of the renal pelvis and ureter will cause colic. Chronic distentions are usually painless. Whether the pain results directly from an irritation of the sensory fibers through stretching or whether it is due to violent peristaltic contractions of the smooth muscle surrounding the passages is not certain, though the latter, from analogy with intestinal colic, seems the more probable explanation.

The pain of renal colic follows a characteristic distribution. It extends over the lumbar region behind, around the flank and above Poupart's ligament into the corresponding testicle or labus major. Pain may also be felt over the anterior and external thigh down to the region of the knee. It traverses the fields of distribution of the eleventh thoracic to the second lumbar spinal segments. This pain may be accompanied by a spasm of the muscles, abdominal and cremasteric, corresponding to a similar level of the spinal cord. This referred pain and muscle spasm, like that occurring in diseases of other viscera, is believed to be due to an irritation of the spinal cord at the level of entrance of the nerves from the urinary passages. Occasionally the pain is associated with an outbreak of herpes zoster over the corresponding region. In other cases hyperalgesia of the skin with painful pressure points can be demonstrated.

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Chapter IX

Disturbances of Heat Regulation—Fever

Physiological Variations in Temperature

(a) *In Different Animals*

With respect to the regulation of the body temperature fundamental differences exist among animals. In the so-called cold-blooded or poikilothermic animals the temperature of the body depends upon the temperature of its surroundings. It rises in warm weather and falls in cold, and the life of such an animal varies accordingly. When warm the animal is active and its metabolic processes proceed at a rapid rate. When cold the metabolism is slowed. and the animal often becomes torpid. In the so-called warm-blooded or homothermic animals, on the other hand, the body temperature is maintained at a fairly constant level and the activities of the animal are more or less independent of its surroundings. Transitions between these two types occur. In hibernating animals and in certain of the lowest mammals the temperature of the body is imperfectly regulated and it descends on exposure to unusual cold.

The mean body temperature maintained by different homothermic animals varies considerably. Among birds the normal mean temperature usually lies between 40° C. (104° F.) and 42° C. (107.6° F.) while normal maximum temperatures may reach 43° C. (109.4° F.) or more. Most mammals have mean body temperatures which are lower than that of birds but somewhat higher than that of man.

(b) *Normal Variations of Temperature in Man*

Although it is customary to fix 37° C. (98.6° F.) as the normal temperature of man it should be remembered that considerable variations occur both in different parts of the body and during different times of the day. The rectal temperature is usually about 0.6° C. (1.0° F.) higher than the mouth temperature and this difference is increased when

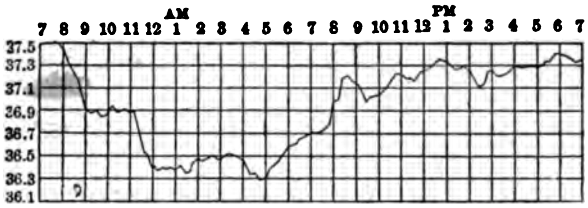

Fig. 103.—Fluctuations in Body Temperature of G. W. H. During "Normal" Day. (After Benedict, Am. Jour. Physiol.)

the mouth has been cooled by taking cold food or liquid, by talking, or by breathing with the mouth open. Even though these temporary changes in the temperature of the mouth be avoided by leaving a thermometer beneath the tongue for five minutes or more, unusual differences between mouth and rectal temperatures are not infrequently encountered; especially in the aged, in the feeble, in those with a poor circulation and in those exposed to cold external temperatures.

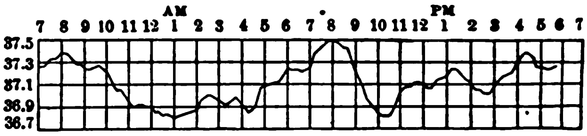

Fig. 104.—Fluctuations in Body Temperature of G. W. H. on the Tenth Day of Inversion of the Daily Routine (Night Work). Note the Incomplete Reversal of the Curve. (After Benedict, Am. Jour. Physiol.)

The normal temperature of man also shows a regular diurnal rhythm. It rises during the day and reaches its maximum in the late afternoon. It falls during the night and reaches its minimum in the early morning hours. (See Fig. 103.) The difference between the maximal and minimal temperatures is usually somewhat over 1° C. (1.8° F.). The cause of this normal diurnal variation in the body temperature of man is not completely understood. Doubtlessly it depends in part upon the muscular activities of the waking hours, for even such a slight difference in muscular activity as is produced by changing from sitting to standing affects the body temperature to an appreciable extent. It is likewise influenced by the taking of food, for diurnal variations are less marked during fasting. It would appear, however, that in man at least the diurnal variations do not depend entirely upon the difference in activity between the sleeping and waking

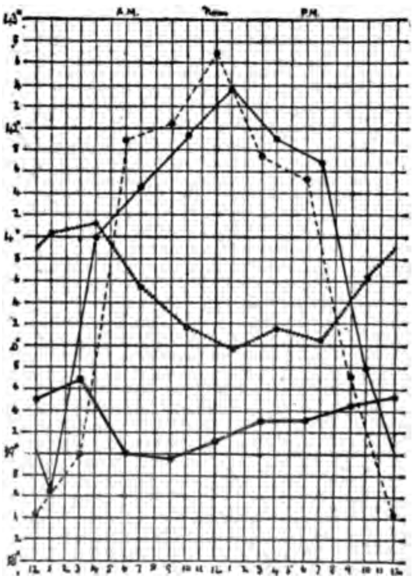

Fig. 105.—The Body Temperature of Birds.[1] Higher Curves from the Thrush, Lower Curves from the Owl. Note that the Nocturnal Life of the Latter Causes a Reversal of Its Temperature Curve. (From Simpson and Galbraith, Jour. Physiol.)

hours, for Benedict and others have found that these variations, though markedly influenced, are not completely reversed by night work, even when this has been followed for years (Fig. 104). In nocturnal birds, however, the reversal of temperature seems to be complete (Fig. 105).

Regulation against Overheating and Overcooling

The Normal Regulation of Body Temperature

The temperature of the body is determined by the relation which exists between the amount of heat produced and the amount of heat eliminated. The heat produced depends upon the basal body metabolism and upon excesses above this resulting from muscular activity, the ingestion of food and possibly other factors (see Total Metabolism). Heat is lost mainly through conduction and radiation from the skin and through evaporation of water from the skin and respiratory tract. Under the usual conditions prevailing in a temperate climate from two to three times as much heat is lost by conduction and radiation as by evaporation; and since during rest the losses by evaporation are about equally divided between the skin and the lungs, it is evident that the skin is the main organ through which heat is lost from the human body.

The delicate adjustment which exists in the body between heat production and heat elimination is under the control of the central nervous system. The principal centers for heat regulation seem to lie ventral to the optic thalami, but they have not been identified with any definite anatomical structures. These centers influence both the production and the dissipation of heat; and they in turn are influenced by afferent stimuli from the skin and mucous membranes as well as by the temperature of the blood which circulates through them.

Regulation Against Overheating

A rise of body temperature results when the amount of heat produced is greater than that eliminated. We have seen that the *production of heat is increased* after the absorption of food, and especially after the absorption of protein food. The extra heat thus liberated is never very great, however, and ordinarily it is promptly eliminated. *Overeating,* and especially the overeating of meats, may increase one's discomfort during hot weather by throwing an extra burden upon heat elimination, but this extra heat rarely, if ever, causes a serious rise in the body temperature of normal individuals. *Muscular activity,* on the other hand, may be an important cause of overheating. The total metabolism of the body may be increased from five to eight times the normal resting metabolism during brief periods of violent exercise and increases of two or three

times the normal are not uncommon during moderate exercise. This increased heat production from exercise not infrequently affects the body temperature. Even under conditions which are favorable for heat elimination moderate exercise may raise the rectal temperature 1° or 2° Fahrenheit. An equilibrium, however, is usually established at this new level and during continuance of the work there is no further rise. The extra heat is eliminated by an increase in the radiation, conduction and evaporation from the surface of the body and also by more rapid and deep breathing. Where the conditions for heat elimination are unfavorable, exercise may cause a serious elevation of body temperature. This has been observed particularly among soldiers who have marched during hot weather while dressed in heavy clothing.

In the dog, where perspiration is almost absent, excessive heat is eliminated mainly by the evaporation of moisture from the tongue and mouth. When overheated the dog opens his mouth, allows his tongue to hang out and breathes very rapidly. If this evaporation is prevented by having the dog breathe through a cannula inserted into the trachea, exercise raises the body temperature to an unusual degree and may cause death from heat stroke.

In man disturbances of temperature regulation may result from diseases of the skin. The loss of skin perspiration in patients with general ichthyosis lessens their ability to regulate against overheating. Exposure to heat or muscular activity may raise the temperature of such patients to an unusual degree. According to Block, these patients compensate to some extent for the absence of perspiration by breathing more rapidly, thus increasing the evaporation from the respiratory surfaces, in a manner analogous to that used by the dog.

We have seen that *heat elimination* is ordinarily accomplished mainly through radiation, conduction and evaporation. The amount of heat lost by conduction and radiation is determined in part by the temperature of the skin, and this in turn by the rate at which the blood circulates through the cutaneous vessels. The circulation in the periphery of the body is very sensitive to changes which affect heat regulation. When exposed to room temperatures sufficiently high to cause moderate feelings of warmth the blood flow through the arm usually increases to about twice the normal. It is evident, however, that if the external temperature is higher than that of the body heat losses by radiation and conduction necessarily cease. Under such circumstances evaporation becomes the sole method of heat elimination. Since the rate of evaporation depends mainly upon the *humidity of the air,* the latter plays an important part in the physiological effects of warm climates. From the physiological standpoint the wet bulb thermometer gives a far better indication of the effective heat than does the ordinary dry bulb thermometer. When the humidity is low evaporation takes place at a more rapid rate and far

higher temperatures can be borne. Movements of air also assist evaporation from the skin and excessive heat is better borne when the air is in motion. Protection against overheating in tropical weather is, therefore, accomplished mainly by an increased activity of the functions which govern heat dissipation. At the same time, however, the individual usually feels relaxed, restricts his exercise, and eats less; all of which diminish heat production, and lessen the danger of overheating.

We have seen that in man the regulation against overheating is effected mainly by a dilatation of the cutaneous blood vessels and by an increase in the perspiration. These reactions are under the control of the central nervous system and they do not take place in an extremity which has been separated from its central nervous control. The nervous centers seem to be guided in this regulation against overheating by two factors:

(1) The temperature of the blood coming to them, and

(2) Reflexes from the warm skin.

If the temperature of the nervous centers be raised either by warming the carotid blood going to the brain or by the direct application of

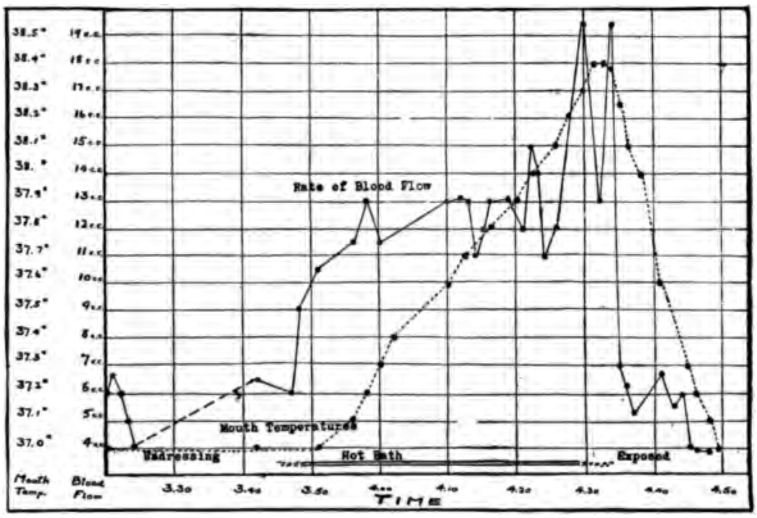

Fig. 106.—The Relation Between the Mouth Temperature and the Blood Flow in the Arm During a Hot Tub Bath. Note that the Rate of Flow Rose at the Beginning of the Bath Before the Mouth Temperature Showed a Change; Also that the Rate Fell When the Water Ran Out, While the Mouth Temperature Was Still Above 38° C. These Effects Were Due to Reflexes from the Skin Produced by the Heat and Cold Respectively. The Arm Studied Was Not Immersed in the Water. (After Hewlett, Van Zwaluwenburg and Marshall, Arch. Int. Med.)

heat through small tubes introduced into the region of the corpora striata, the various physiological changes that characterize the regulation against overheating take place. In rabbits the skin vessels dilate, in dogs the

characteristic rapid breathing appears. Artificial heating of certain parts of the brain may, therefore, lead in animals to a lowering of the general body temperature. Apparently in man also the temperature of the blood is an important factor in setting in operation the mechanism for increasing its heat losses. Thus, Stern showed that when a person is immersed in a moderately warm bath sweating does not occur at first but appears when the body temperature has been raised from 0.1° to 0.8° C. (0.2° to 1.4° F.).

On the other hand, it is certain that in man reflexes from the skin play an important part in setting in operation the mechanisms for heat loss. Filehne showed that by being partially immersed in a hot bath he could cause an outbreak of perspiration even though the body temperature remained constant or fell slightly. Furthermore, as may be seen in Figure 106, the blood flow through the arm is promptly accelerated when the body is immersed in hot water, long before the mouth thermometer shows any appreciable rise of temperature. In this experiment the reflex effect produced by the stimulation of the skin by heat appeared to be more potent in increasing the blood flow in the arm than did the later rise of body temperature. During muscular exercise, on the other hand, it is not improbable that the chief stimulus to the heat regulatory centers may arise from the elevated temperature of the blood, for the skin is often cool from perspiration.

Sunstroke

Slight rises of body temperature are not infrequent as a result of exercise, but if reasonable opportunities are present for heat losses, these rises never become dangerous. Rises may also be produced artificially in normal animals or men by placing them under conditions which prevent heat losses from the body. This may be done most simply by subjecting them to moist heat, thus preventing heat losses by conduction, by radiation and by evaporation. If a normal man be immersed up to his neck in a hot bath the body temperature may readily be raised to 38° C. (100.4° F.) or 38.5° C. (101.3° F.) without great discomfort; and by continuing the immersion it may be raised to 40° C. (104° F.) or, indeed, to dangerous heights.

These hyperthermias produced by exposure to moist heat have many points in common with the effects of heat which are frequently observed in those living in hot climates. In the milder cases of heatstroke, the so-called *heat prostrations,* the patient usually complains of headache, dizziness, pains in the back and limbs, nausea, and thirst. He is unable to work and sleeps poorly. His temperature, though occasionally subnormal, is as a rule moderately elevated, from 37.3° C. to 40.4° C. (99.1°–104.7° F.). In the so-called *asphyxial form* of sunstroke, which is relatively uncommon, the patient becomes unconscious with a temperature showing about the same

range as in heat prostration. The *more severe forms of sunstroke* are always associated with a marked increase of the body temperature. In these cases there is frequently a history of prodromal symptoms similar to those present in heat prostration, which prodromes are then followed by unconsciousness. The body temperature rises to heights that are rarely approached during acute infections. From 40° to 44° C. (104°–111.2° F.) are common, while temperatures of 46° C. (114.8° F.) and over have been observed. When the temperature does not pass 44° C. (111.2° F.) recovery is fairly frequent under vigorous antipyretic treatment but when the temperature exceeds this limit recoveries are rare. Patients showing these high temperatures are as a rule deeply comatose and have lost control over micturition and defecation. The skin is often dry, it may be hot or cool, and its color may be pale, livid or cyanotic. A dry, cool or pale skin indicates that a maximum heat dissipation is not taking place, and it shows that the normal mechanism which regulates against overheating has become deranged.

Among the most common causes of sunstroke are continued high temperatures with high humidity, and continued exercise during warm weather while wearing unsuitable clothing. Heat prostrations, though usually of the milder type, are relatively common when soldiers march long distances in hot weather and in full uniform. They are common, too, in large cities during prolonged periods of hot weather.

Predisposing Factors.—Many facts indicate that in clinical heatstroke we are dealing not with a simple overpowering of a normal temperature regulation but with the overpowering of a relatively inefficient mechanism and ultimately with a derangement of this mechanism. It is well known, for example, that heatstroke is more prone to attack certain individuals, presumably because their regulation against excessive heat is less perfect than the average. Persons of low vitality and especially fat individuals with poor circulations are liable to sunstroke. By far the most important predisposing cause is the abuse of alcohol. The majority of heatstroke cases in larger cities occur in moderate to heavy users of alcohol, which drug seems to lessen the effectiveness of the regulation against overheating. A weakening of the mechanism is also the probable explanation of the fact that in large cities heatstrokes do not occur with any high degree of frequency during the early days of a hot spell. Continuance of very hot weather seems to break down the ability of certain individuals to resist it. The dry or cool skin present in certain patients suffering from heatstroke also indicates a faulty elimination. Finally, after the patient's temperature has been reduced to the normal or nearly normal level by the vigorous use of hydrotherapy, it is common for the patient to show occasional or continuous fever for days and even weeks after the acute hyperpyrexia has subsided. During this time the body temperature may be exceedingly sensitive to external influences and it may rise with every

increase in the external temperature. For years after, such patients may show an increased sensitiveness to heat. It is evident, therefore, that the hyperpyrexial form of heatstroke is usually associated with and is followed by marked disturbances in the heat regulation of the body. The overpowering of a normal or weakened regulation by excessive heat deranges the nervous centers which regulate heat losses.

Regulation Against Overcooling

Man is ordinarily exposed to temperatures considerably lower than that of the body; and for this reason regulation against overcooling is in more frequent demand than regulation against overheating. As a matter of fact, a much greater range of low than of high temperatures can be tolerated. Protection against heat losses is assisted by a thick layer of fat beneath the skin. In animals the fur and other coverings of the body serve to prevent excessive dissipation of heat and by means of clothes man is enabled to interpose an artificial resistance to cold. Aside from these factors an individual exposed to cold has at his disposal two general methods for maintaining his normal body temperature. The first of these, the so-called *physical regulation,* consists of restricting the heat losses by diminishing the caliber of the skin vessels so that less blood flows through the periphery of the body. Exposure to moderate cold reduces the blood flow through the arm to one-half or less of what it is at comfortable external temperatures. Under these circumstances the skin may appear blue or white according as the cutaneous capillaries contain more or less blood; but in either case the circulation through them is very slow. The second method of regulating against overcooling, the so-called *chemical regulation,* is accomplished by an increased metabolism in the muscles. When the body is exposed to moderate external temperatures this chemical regulation is not operative and protection against overcooling is governed solely by physical means. When exposed to lower temperatures, however, the physical regulation may be insufficient. It is well known that persons ordinarily exercise or shiver when exposed to excessive cold. The heat thus liberated is used to maintain the body temperature. Extra heat may also be derived from the ingestion of food and persons withstand cold better after a full meal than when fasting. Whether an increased production of heat may occur on exposure to cold through increased muscular activity of a different type than very slight shivering is not yet settled.

As with the regulation against overheating, so here also, we have a control of the mechanism by the heat regulatory centers of the central nervous system. If cold be directly applied to these centers they regulate so as to retain heat in the body and thus increase the body temperature. They are also influenced by sensory impulses from the skin, for if the latter be suddenly cooled a reflex constriction of the cutaneous

vessels of the body occurs almost immediately. Indeed, a brief cold bath not infrequently causes a rise of body temperature because of the increased muscular activity and constricted skin vessels that result from the cutaneous stimulation by cold.

Freezing

We have seen that when a warm-blooded animal is exposed to cold a reduction of the body temperature is prevented partly by diminishing heat dissipation and partly by increasing heat production. Under certain circumstances, however, this protective mechanism is broken down and the bodily temperature then falls. In hibernating animals such a fall is physiological and during the winter sleep they live with all the body functions markedly depressed and with the body temperature not far above the freezing point of water. In most warm-blooded animals, however, any marked reduction of body temperature causes death. It is usually stated that for mammals body temperatures of 20° C. (68° F.) or below are incompatible with life, but life is seriously endangered, in the rabbit at least, when the body temperature falls below 30° C. (86° F.). Reincke has reported a remarkable case where a drunken man after exposure to cold was admitted to the hospital with a rectal temperature of 24° C. (75.2° F.) and yet recovered.

Predisposing Factors.—Among the factors which reduce the ability of an individual to withstand cold are absence of proper clothing, lack of food, and muscular weakness. Small animals, on account of the relatively large surface of their bodies in proportion to the weight, have in general a less perfect regulation against cold than have large animals. If a rabbit, guinea-pig or cat be tied on its back and exposed to a moderately cold room its temperature falls owing to its extended position and lack of exercise, and death may result. As might be expected, this cooling proceeds more rapidly if the fur has been cut away. Infants and especially the new-born also resist cold poorly. In the latter this lack of resistance seems to depend, not so much upon the small size, as upon an imperfect action of the heat regulatory mechanism shortly after birth. Alcoholism is also an important factor in the etiology of freezing just as it is in the etiology of sunstroke. The dilatation of the cutaneous vessels caused by alcohol produces a feeling of warmth but at the same time it increases the heat losses and in this way tends to reduce the body temperature. The most important action of alcohol, however, is upon the nervous centers, producing somnolence and a less perfect nervous control of the mechanism which guards against heat losses.

Symptoms.—The initial symptoms produced by exposure to cold consist of increased muscular activity which is manifest either by increased exercise or shivering. The mind is alert and the individual often feels

unusually energetic. When, however, the temperature of the body begins to fall and there is danger of freezing, the alertness and muscular activity are replaced by muscular weakness and fatigue, stiffness in the limbs and drowsiness, which are followed by deepening coma. The muscular relaxation, somnolence and coma are evidence of a breaking down in the normal body regulation against cold, for they indicate that the overproduction of heat from muscular activity has ceased. The body metabolism which at first is increased through the increased muscular activities eventually becomes reduced, just as the metabolism of a cold-blooded animal lessens when its temperature has fallen on account of exposure to cold surroundings.

The Effect of Spinal Cord Section

It has been known since the time of Benjamin Brodie that marked variations in the temperature of the body are apt to follow injuries that cause a division of the cervical spinal cord. The temperature may be either raised or lowered. Gardiner and Pembrey have collected from the records of Guy's Hospital twenty-four uncomplicated cases of spinal cord injury in man where the temperature was disturbed. Of these, nineteen showed hyperthermia and five showed hypothermia. Extraordinary temperatures may occur in such patients. In Benjamin Brodie's patient, for example, the temperature rose to 43.9° C. (111° F.) before death. On the other hand, it may fall to 26.7° C. (80.6° F.) or even lower. While in man a rise of temperature is more common than a fall, in animals section of the cervical cord is ordinarily followed by hypothermia. Only in the case of large animals or where care has been taken to maintain unusually warm surroundings does the temperature rise as it does in the majority of clinical cases.

The causes of the temperature changes which follow high section of the spinal cord are now fairly well understood. Rises of temperature are due in part to the irritation of the nervous tissues at the site of the lesion and are more apt to follow transverse lacerations than clean cut sections. Most important is the fact that such injuries sever the nervous paths leading to the main tissues that regulate the body temperature, particularly the muscles and the skin. The muscles in the paralyzed area become flaccid, the skin circulation is at first increased and later diminished, and the sweat glands soon cease to be active. All have lost their connections with the nervous centers which govern the body temperature. The temperature of a rabbit with the spinal cord severed in the lower cervical region is influenced by external temperatures in much the same way as is the body temperature of a cold-blooded animal. At a certain external temperature its body temperature is normal but the latter rises and falls with slight external changes. If the cord is cut in the upper

thoracic region the regulation against cold, though less perfect than normal, is far better than when the cervical cord is divided. (See Fig. 107.) According to Freund, this marked difference between the effect of a lower cervical and an upper thoracic operation is due to the severance of sympathetic paths leading to the abdominal viscera.

When a warm-blooded animal is exposed to cold there is an increased metabolism due to muscular activity. Pembrey has shown that after division of the dorsal cord of mice the metabolism fails to show this characteristic change when they are exposed to cold and may even

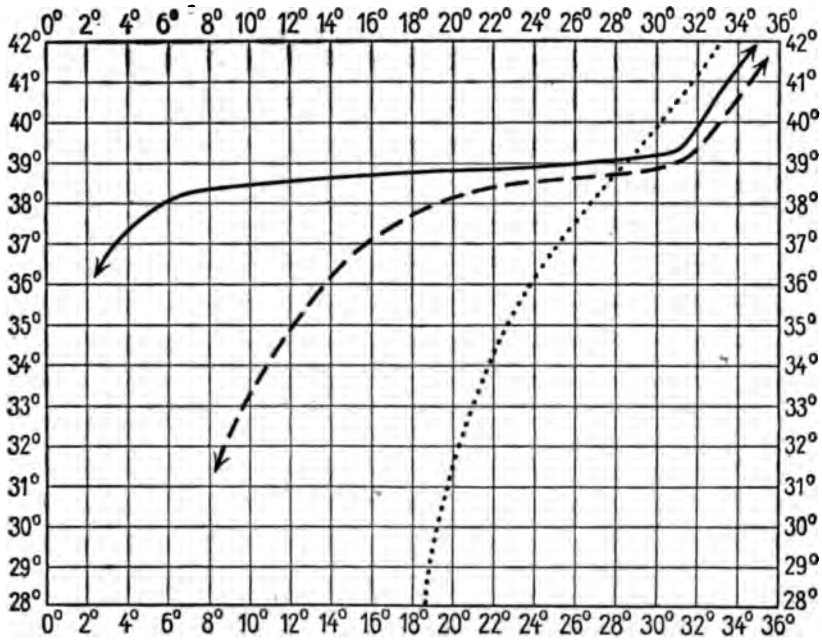

Fig. 107.—The Effect of External Temperatures Upon the Body Temperatures of Rabbits. Continuous Line Normal Animals, Broken Line After Section of the Dorsal Cord, and Dotted Line After Section of the Cervical Cord. Note that the First Withstand Low External Temperatures While the Last Behave Like Poikilothermic Animals. (After Freund and Strasmann, Arch. f. exper. Path. u. Pharmak., published by F. C. W. Vogel, Leipzig.)

show the opposite change, with temperature and metabolism varying in the same direction, just as happens in cold-blooded animals. In the paralyzed portion of the body where there is no central nervous control over heat production and heat loss, temperature regulation is completely absent; in the unparalyzed portion it takes place normally with shivering when the body temperature falls and sweating when it rises. The resulting body temperature depends upon the combination of these two factors. In small animals with a relatively large body surface the temperature falls when the animal is exposed to ordinary room temperatures. In man with body surface relatively small in proportion to his weight the tempera-

ture is more apt to rise; and particularly so if, as so frequently happens, he is kept unusually warm after the accident. The changes in body temperature which follow section of the cervical spinal cord are, therefore, due mainly to a loss of the normal heat regulation over an extensive portion of the body. Hyperthermias of this type differ from true fever in that the latter, as we shall see, depend upon a perversion of the temperature regulation rather than upon its abolition.

The Conception of Fever

Definition.—The term fever, though in common use, is by no means easy to define. Our conception of fever is based upon the reaction seen in infectious diseases. This reaction consists in part of an alteration in the body temperature together with changes in the mechanisms which control this temperature. The reaction consists also of various other responses by the body, such, for example, as the formation of antibodies. The term fever is applied particularly to the reactions which have to do with the elevation of body temperature and in the broader sense it may be applied to all temperature reactions which resemble those occurring in infectious processes. As we shall see, fever in this broader sense may be due to many causes other than infection. That due to the parenteral introduction of foreign proteins or to the unusual destruction of protein substances within the body is most closely related to infectious fever. The rise of temperature following the injection of certain chemicals and that following injury of the base of the brain are also closely related, inasmuch as the mechanism of temperature changes is similar to that which prevails in infections.

On the other hand, certain forms of hyperthermia are distinctly different from infectious fever. This is true, for example, of the rise of body temperature induced by exposure to moist heat where the normal heat regulation of the body is broken down by external conditions. Nor can the excessive temperatures which frequently follow lesions of the upper spinal cord of man be called fevers in the sense that we have used the term; for these are caused by a *lack* of thermic regulation which is similar to that present in cold-blooded animals; whereas, in true fever, heat regulation is *present* but *perverted.*

Types of Fever

It is customary to divide fevers according to the height of the temperature into the low, high and excessively high fevers. It is customary to divide them furthermore according to the constancy with which the elevated temperature is maintained. When the temperature is maintained at a fairly constant level for several days with fluctuations not

much greater than those occurring in normal individuals the fever is spoken of as being *continuous.* When the fluctuations are considerably greater but still the temperature remains above the normal the fever is described as *remittent.* When finally the fever touches normal at sometime in the day but goes considerably above normal at other times the fever is spoken of as being *intermittent.* The rise in temperature in fever may be gradual and steplike or it may be very sudden. In the latter case chilly sensations or a shaking *chill* are usually present. It may fall slowly by *lysis,* or it may fall suddenly by *crisis.*

Heat Regulation in Fever

Considerable interest attaches itself to the mechanism whereby the temperature of the body is raised or lowered during febrile changes of temperature and to the mechanism whereby an elevated but fairly constant temperature is maintained.

Sudden Changes of Temperature

The phenomena attending the *febrile chill* are striking. The skin becomes pale or cyanotic and often feels cold to the touch. The peripheral circulation is slowed and the insensible perspiration is diminished. The individual experiences sensations of great chilliness and there may be severe shivering. Everything conspires toward an elevation of the internal temperature of the body. By means of shivering excessive quantities of heat are set free within the body; by means of the reduced peripheral circulation the heat losses are checked. Although the skin is cold, the temperature within the body rises rapidly and may reach 40° C. (104° F.) within an hour or two.

During the rapid fall of temperature which occurs during a *febrile crisis* the opposite manifestations occur. The skin is warm and moist and there is often a profuse sweat. The skin circulation is increased. During this time also the rate of body metabolism descends to a low level. Less rapid fluctuations in tem-

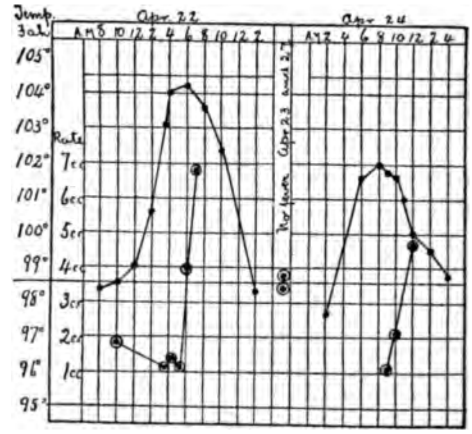

Fig. 108.—The Relation of Sudden Changes in Febrile Temperature (Upper Curves) to the Blood Flow in the Arm (Lower Curves). On April 23 the Temperature Was Normal and the Blood Flow About 3.5 c.c. per 100 c.c. of Arm Volume per Minute. During the Rising Temperature and Somewhat Thereafter the Blood Flow Is Slow; During the Febrile Fall the Blood Flow Is Rapid. (From Hewlett, Heart.)

perature cause similar though less marked changes. The circulation in the arm is relatively slow during rises of temperature and is relatively fast during falls. (See Fig. 108.)

So far as rapid changes of febrile temperature are concerned, therefore, the mechanism which is brought into play in order to produce these changes apparently differs in no particular from the mechanism that is used by the normal individual in maintaining his temperature constant under varying conditions. In the febrile chill with the constricted skin vessels and increased muscular activity we have a counterpart of the normal regulation against cold. Or to express it in another manner, the *phenomena of the chill* are such as one would expect if for some reason the body temperature of a normal individual were suddenly reduced and his centers were endeavoring to raise it. Similarly, the *phenomena of the crisis* are in every way comparable to those which follow moderate overheating of the body by violent exercise or by a hot tub bath. They are those which are used by the normal individual to regulate his body temperature downward. In fever, chilliness and shivering are followed by an elevation of temperature, a regulation to a higher level; sweating, on the other hand, means a fall of temperature, a regulation to a lower level.

Continuous Fever

During continuous fever heat production and heat dissipation are of necessity equal so long as there is no variation in the body temperature. Rises or falls of temperature mean that the two fail to balance. Why should the temperature remain elevated in fever? Is it due primarily to an increased combustion within the body? Is it due to a restricted heat dissipation? Or is it due finally to a disturbance in the regulating centers so that in spite of variations in production or in dissipation the new temperature is maintained in much the same way as is the normal temperature? Studies on patients have shown that there is, as a rule, *a moderate increase in the total heat production* during the continuous periods of fever. As a rule, this increase is from twenty to thirty per cent above the normal but under exceptional circumstances it may rise to fifty or sixty per cent and possibly even more. In some cases, however, and particularly in low and long-continued fevers and in weakened individuals, the heat production may be normal or even subnormal. The varying degrees and the causes of the increased heat production usually present in fever will be discussed later, but it may be stated in passing that it is due in part to the increased body temperature and is thus in part a result rather than a cause of the high temperature.

Whatever may be the chief cause of the increased heat production commonly present in fever, it is certain that one cannot explain the febrile rise of temperature from this increased heat production alone.

The normal body can and frequently does produce and eliminate far larger amounts of heat without a significant rise in temperature. During moderate exertion, for example, two to three times the normal heat is produced within the body and yet this is eliminated with ease. The insignificant rise in body temperature produced by exercise promptly disappears after its cessation. During exercise the chief source of the extra heat is an increased combusion of carbohydrates. That the body may also eliminate heat derived from other sources is evident from the fact that an increased heat formation of sixty per cent produced by feeding protein to dogs is eliminated with ease.

When we compare these examples of the normal capacity for heat elimination with the amounts of heat produced in the body during fever it becomes evident that an overproduction of heat can play but a small part in producing the febrile elevation of temperature. Far more important is a *relative insufficiency in the heat-elimination.* As a matter of fact, the blood flow through the feet and through the arms is usually somewhat slower than normal in continuous fevers and the insensible perspiration is but moderately increased. If the temperature of a normal individual be raised artificially to 38° C. (100.4° F.) his heat regulatory mechanism responds with an enormously increased blood flow through the extremities and with profuse sweating. The patient with fever, on the other hand, with an equally high or higher body temperature, usually shows a diminished skin circulation and no unusual activity of perspiration.

This relative inactivity of the mechanism for heat dissipation does not mean that the febrile patient is unable to dissipate heat. If he be artificially heated above his febrile temperature he reacts exactly as the normal individual does. Stern has shown that when a febrile patient is immersed in a warm bath a further increase in his body temperature of 0.1° to 0.8° C. (0.18° to 1.4° F.) will cause sweating just as it does in the normal individual. If exercise be taken the extra heat liberated within the body is for the most part dissipated in a normal manner. The insensible perspiration after taking food is increased to about the same extent in febrile and in normal individuals. R. Hirsch has shown that in the trypanosome fever of dogs the administration of quinin may reduce the heat production to the normal and yet owing to a corresponding reduction of heat elimination the febrile temperature may remain constant. Finally, the febrile patient maintains his body temperature against agencies which tend to reduce it just as the normal man does. When he is exposed to cold his skin vessels contract and he shivers.

It is evident, therefore, that in continuous fever there is no absolute insufficiency on the part of the various agencies which control heat production and heat dissipation. Heat is produced and is lost in response to agencies which might change the febrile temperature exactly as it is in the normal individual. *The febrile temperature is primarily due not to an*

increase in heat production or to an absolute inefficiency in heat dissipation but to a lack of adjustment between the two. According to Liebermeister, the heat regulation in fever behaves as if the regulatory centers were "set" to maintain the body temperature at a new level, which new level is maintained in much the same manner as is the normal temperature. More recent writers speak of an increased excitation or excitability of the heat centers which causes them to regulate the body temperature at the new and higher level.

Imperfect Heat Regulation in Fever

Although the heat regulation in fever is carried on by the same mechanism as in the normal individual there are many reasons for believing that it is less perfectly adjusted than in health. The healthy adult, for example, is far more resistant to the effects of the cold bath than is the patient with fever. It is more difficult to reduce his temperature and the reductions are more transient. The same is true with regard to the effect of antipyretic drugs. Marked differences exist among fever patients or in a given patient at different times, in regard to the constancy with which the febrile temperature is maintained when the body is exposed to disturbing influences. This is particularly well seen on the charts of typhoid fever patients who have been treated with cold baths. During the earlier and more continuous portions of fever the reductions of temperature produced by the baths are relatively slight and transient. In the third week of the disease, however, when the temperature is beginning to show wider diurnal fluctuations, baths usually produce much more marked and prolonged remissions in the fever. Furthermore, the remissions are most marked at times when the febrile temperature itself shows a downward tendency.

Not only is the febrile regulation against antipyretic influences less perfect than the normal but it seems probable that extra heat produced within the body is less perfectly eliminated by fever patients than by normal individuals. It is well known, for example, that patients with tuberculosis and convalescents from typhoid fever not infrequently show transient rises of temperature after moderate exercise. In such cases, it is difficult, of course, to exclude reinfection or intoxication as a cause of the rise of temperature. Nevertheless, it seems probable that, in some cases at least, such a rise of temperature may simply be an exaggeration of the rise of temperature which occurs in normal individuals after exercise. The unusual rises in these patients may be due to an unstable condition of the heat regulatory centers and an imperfect elimination of the heat set free by exercise. The same may be true of certain rises of temperature which occasionally occur in convalescent typhoid patients after a hearty meal.

Metabolism in Fever

Nitrogenous Metabolism

It has long been known that during fever there is usually a *negative nitrogen balance.* More nitrogen is eliminated in the excreta than is taken in the food. Efforts to cover these nitrogen losses by feeding increased amounts of protein have, as a rule, led to simultaneous increases in the output of nitrogen in the urine and the nitrogen balance has remained negative. The amount of protein which is lost from the body may be very considerable. In some cases it is equivalent to a daily loss of from 200 to 500 grams of muscle tissue a day. In Staehelin experiments with animals infected with surra he estimates that over one-fifth of the protein of the body was lost during the course of the disease. The rate of nitrogen loss during fever does not follow very accurately the height of the temperature. In some cases it is pronounced although the fever is not high and it may be relatively slight with a high fever. Of particular interest is the fact that there may be a marked increase in the excretion of nitrogenous material in the urine immediately following the close of the fever, the so-called epicritical excretion. During convalescence there is usually a nitrogen retention and a replacement in the body of the protein lost during the febrile period.

The increased excretion of total nitrogen during fever is usually accompanied by an increase in the excretion of uric acid and purin bases, as well as by an increase in the excretion of creatinin. The increased excretion of purin bodies indicates an increased catabolism of the nucleoproteins of the body. The increase in creatinin indicates destruction of muscular tissue. The increase in these bodies, therefore, is a further evidence of a loss of living substance from the body during the course of the fever.

Various efforts have been made to demonstrate that in fever there is not only a quantitative increase in protein destruction but that the protein catabolism is qualitatively abnormal. Krehl and Matthes, for example, found albumoses in the urines of fever patients, and at one time they believed that these played a part in causing the rise of temperature. Subsequent work has shown, however, that these bodies may occur in the urines of non-febrile patients and that they are absent from many febrile urines. Other evidence in favor of the view that the protein metabolism is qualitatively altered has been sought from the abnormally low respiratory quotient found in fever by certain investigators and from a change in the relation between the carbon and the nitrogen in the urine. Both of these findings are, however, doubtful and at the present time there seems to be no proof of a definite qualitative change in the character of the protein metabolism during fever. That such a change may be present

is suggested by the extensive degenerations in the tissues seen microscopically, by the epicritical elimination of urea which may well be derived from degenerated tissue, and by the diazo-reaction which is believed by von Fürth to depend upon the presence of abnormal products of protein catabolism in the urine.

The *cause* of the increased protein decomposition in fever has been of great interest because it has seemed possible that this might be related in some way to the production of the febrile reaction. All observers recognize that the increased protein metabolism in fever is due to a number of causes. Among these causes may be mentioned the increased temperature of the body. Experiments on animals as well as on men have shown that in certain cases when the temperature of the body is artificially raised the protein metabolism is increased. According to Linser and Schmid, this increase in man begins when the body temperature has reached 39° or 40° C. (102.2° or 104° F.) and beyond this point it may become very marked. Graham and Poulton, on the other hand, were unable to obtain definite increases. A second factor in the causation of the increased protein metabolism during fever is partial starvation. Partly on account of the poor appetite of febrile patients and partly on account of a general desire not to overtax their digestive capacity, it has been customary to furnish diets which are markedly deficient in nutriment. The number of calories present in most fever diets (1,200 calories or less) will not cover the needs of a normal individual; and since the febrile patient has a basal metabolism which is usually 15 to 40 per cent more than the normal, he develops a condition of marked undernutrition. Under such circumstances his body tissues must be consumed in order to supply his caloric needs. According to Grafe, the increased protein metabolism under such circumstances does not differ essentially from what one obtains in normal individuals who are subjected to a similar grade of undernutrition. A further cause for increased elimination of nitrogen in the urine during fever is a resorption of inflammatory exudates, such as takes place during the course of pneumonia, acute rheumatic fever, pleurisy and other conditions.

The question remains, whether, after allowing for the increase in protein metabolism which may be caused by the high temperature, by the partial starvation and by the resorption of exudates, there still exists an abnormal protein decomposition which is due to some toxic cause and is more or less characteristic of fever. This doctrine of a *toxic protein destruction* has played an important rôle in discussions as to the nature of fever. We have seen that the attempt to prove an abnormal protein catabolism by demonstrating unusual end-products such as albumoses has not met with great success. The toxic theory has also been supported by the practical difficulties encountered when one attempts to maintain nitrogenous equilibrium in fever patients. Shaffer and Coleman have,

however, demonstrated conclusively that it is possible to maintain patients with typhoid fever in nitrogenous equilibrium by giving them a diet of very high caloric value which also contains large amounts of carbohydrates. They demonstrated, furthermore, that this diet not only maintains nitrogenous equilibrium but that it reduces the abnormal excretion of creatinin which, as we have seen, is probably derived from a breaking down of the muscular tissue. It seems probable, therefore, that this diet protects the body proteins from disintegration, for these results could hardly be explained on the basis of a retention of food proteins or of the products of protein decomposition within the body. These observations have since been confirmed by Roland and by others with diets which were believed to cover merely the caloric requirements of the febrile patients. It is evident, therefore, that the nitrogen losses of fever can be overcome, in part or in whole, by a liberal use of properly selected carbohydrate food. The doctrine of a toxic or essential protein destruction in fever is, therefore, no longer supported by the argument of an essentially negative nitrogen balance. Nevertheless, as R. A. Kocher has shown, a complete analogy to the normal has not been proven, for the abundant use of carbohydrate food will not give as low a protein minimum in fever as in health (page 233). There appears, therefore, to be a specific protein destruction in fever.

Non-nitrogenous Metabolism

We have already stated that the total metabolism in fever is, as a rule, moderately increased. According to Grafe, this increase usually averages between twenty and thirty per cent above the normal basal metabolism for the same individual. If, however, one could compare the metabolism in fever with that of the same individual during an equal degree of undernutrition this percentage increase would be somewhat greater. The increased metabolism during fever rarely exceeds forty or fifty per cent over the normal. In some cases, and especially in long-continued low fevers with advanced inanition, the rate of metabolism may be lower than the normal. Here again, however, it is difficult to compare the figures obtained with those of the same individual in a similar stage of inanition. This increase in the total metabolism is due, in part at least, to the accelerating effect of the increased body temperature upon its chemical processes. By overheating the body with moist heat Sutton obtained an increase in the rate of total metabolism equal to or greater than the increases which have usually been observed in fevers of corresponding height.

We have seen that in fever there is an increase in the protein decomposition which can usually be covered by a proper diet. On the usual fever diet about eighty per cent of the heat production is derived from non-nitrogenous material. Grafe calculates that the greatest proportion

of this is supplied by the combustion of fats. It is probable that the carbohydrate reserves of the body are rapidly depleted and that the considerable fat metabolism is due to the partial starvation. With an adequate supply of carbohydrates the combustion of fats as well as of proteins can be restricted.

Acidosis

In fever evidence of acidosis is frequently present. Acetone bodies may be found in the urine, the urinary ammonia is often increased and the tension of carbon dioxid in the alveolar air is often diminished. In so far as this acidosis depends upon the acetone bodies it is probable that its cause, like that of most other forms, is the inanition, with increased combustion of fats and diminished combustion of carbohydrates. Graham and Poulton have shown that if the body be overheated during partial starvation a striking increase in the elimination of the acetone bodies results, probably on account of an increased combustion of fats. This does not occur, however, if the body be well supplied with carbohydrates. It seems probable, therefore, that a diet rich in carbohydrates and of sufficient caloric value would diminish and perhaps eliminate the acidosis due to acetone bodies which occurs during fever. Whether there are in addition other sources of the acidosis of fever has not been settled.

Salt and Water Retention

It is an old observation that the *excretion of chlorids* in the urine is frequently reduced to a remarkable extent during the febrile state. This is particularly true of lobar pneumonia and it is more marked in pneumococcus than in influenzal pneumonia. It is associated with a reduced elimination of sodium and calcium. The reduction of chlorids may occur so promptly that it cannot be attributed to partial starvation or to a diet poor in chlorids, although such diets may contribute to a continuance of the small chlorid excretion during the fever. Furthermore, when sodium chlorid is administered to febrile patients it is retained in the body to a greater degree than when it is administered to normal individuals. The exact cause of this retention and the portion of the body in which the sodium chlorid is deposited are not known. This retention of salt during infectious diseases seems to be associated with a simultaneous retention of water. It is an old view that such a *retention of water* occurs during acute infections and that with the crisis there is an unusual loss of weight due to an elimination of this extra water. Studies of the water balance in fever are carried out with difficulty and much doubt has been expressed concerning the correctness of this view. It is supported, however, by

recent studies of the blood concentration in infectious fevers. These studies have shown that during many infections there is an hydremia or dilution of the blood serum and that with the crisis the hydremia may disappear with a simultaneous elimination of chlorids and a sudden loss of weight due to elimination of water (Fig. 109).

The cause of this hydremia with retention of salt and of water is not well understood. Examinations of the blood during the periods of reten-

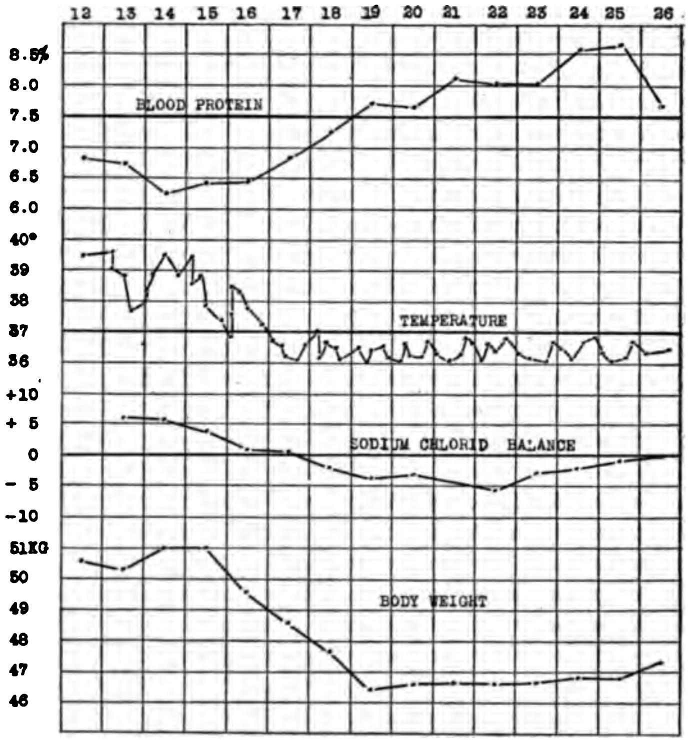

Fig. 109.—Lobar Pneumonia. Note that During the Fever the Percentage of Blood Protein Is Low (Hydremia) and that Salt Is Retained in the Body. With the Fall of Temperature There Is an Increased Excretion of Sodium Chlorid, a Concentration of the Blood and a Rapid Fall in Weight Due to the Loss of Water. (After Sandelowsky, Deutsch. Arch. f. klin. Med., published by F. C. W. Vogel, Leipzig.)

tion by Peabody, by Snapper, and by McLean, have shown, however, that the concentration of sodium chlorid in the blood is abnormally low. It differs, therefore, from the salt retention in nephritis, where, as we have seen, the concentration of chlorids in the blood is relatively high. This would seem to indicate that in fever the fault lies not in a diminished excretory ability of the kidney but in some physical or chemical change in the body which leads to a deposition of salt in the tissues.

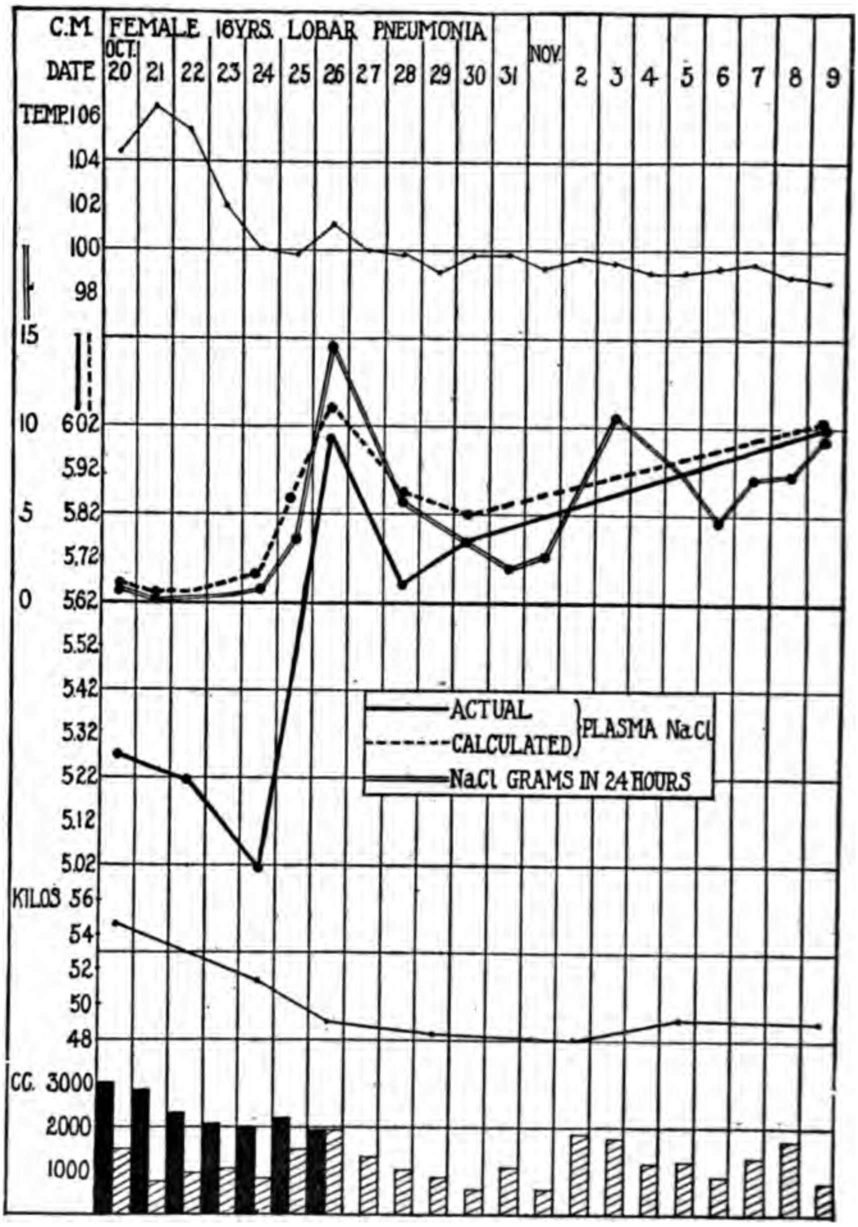

Fig. 110.—Uncomplicated Lobar Pneumonia with Recovery Showing the Water and Salt Metabolism. Note that the Crisis Is Accompanied by a Rapid Fall of Weight (Loss of Water) and by a Rapid Excretion of Chlorids. During the Fever the Chlorids in the Urine Were Markedly Depressed. The Examination of the Blood Showed that the Chlorids in the Blood Were Below What Would Correspond to the Urinary Excretion in a Normal Individual (page 429). This Indicates that the Diminished Excretion Was Not Due to a Renal Insufficiency But to a Withdrawal of Chlorids from the Blood by the Tissues. (From McLean, Jour. Exp. Med.)

Causes of Fever

Lesions of the Central Nervous System

We have seen that in fever the high temperature of the body can best be explained by assuming that the normal relation between heat formation and heat elimination is disturbed. The febrile patient regulates his body temperature at the new level by the same methods that are used normally. This change in heat regulation seems to depend upon changes in the irritability of the heat regulatory center or centers in the brain. This view has received strong support from the rise of body temperature which follows certain experimental nervous lesions. In 1884, Aronsohn and Sachs showed that it was possible to produce an elevation of body temperature in rabbits by puncturing the base of the brain. This so-called *heat puncture* has been successfully performed by numerous observers and on a variety of animals. The importance of the base of the brain for heat regulation has been further demonstrated through the interesting experiments of Barbour, who showed that the direct application of heat to this region throws into operation the mechanism for increasing heat losses with a resultant fall in the body temperature. On the other hand, the direct application of cold to this region throws into operation the mechanism for raising the body temperature. The centers are, therefore, stimulated by cold and depressed by heat. Successful punctures usually pierce the region of the basal ganglia but discussion still continues as to the exact portion of the brain which causes the rise of temperature after a successful puncture. The caudate nuclei, the optic thalami, and the lateral ventricles have each been regarded as the essential region that must be injured in order to produce fever. Isenschmid and Krehl have shown that the cerebrum, the caudate nuclei and the anterior portion of the optic thalami may be removed from rabbits with only a temporary change in the heat regulatory mechanism. When, however, the posterior and ventral portions of the optic thalami were removed their animals lost the ability to regulate the body temperatures and the latter then became subject to external conditions just as happens in the case of an animal whose cervical cord has been cut (page 468).

After a successful heat puncture the rabbit's temperature may show a brief fall. It then rises abruptly, usually attaining a height of from 40° to 42° C. (104° to 107.6° F.), and remains elevated for from two to four days. This rise of temperature is associated with a constriction of the peripheral blood vessels and an increased production of heat within the body. Broadly speaking, therefore, it resembles the hyperthermia of infections. Various attempts have been made to establish fundamental distinctions between the hyperthermia of heat puncture and that of infectious dis-

eases. It has been claimed, for example, that in heat puncture the excessive heat produced is derived mainly from a combustion of the carbohydrates derived from hepatic glycogen, whereas in fever we have a more marked combustion of proteins. According to Senator and Richter, however, it is possible to get an increased temperature from puncture even though the glycogen store in the body is depleted. Furthermore, the increased protein metabolism is by no means so constant a characteristic of infectious fever as was formerly believed. It has also been claimed that the rabbit does not regulate its temperature after thermic puncture as perfectly as in infectious fever; yet this difference may be quantitative rather than qualitative.

In a broad way, therefore, the rise of temperature produced by puncture of the base of the brain resembles that which occurs during infectious processes. Essential and undoubted differences have not been established and the most probable explanation of the rise of temperature during infectious diseases is that the heat regulatory centers in the midbrain are stimulated by some products of infection. That the cause of the febrile rise of temperature acts upon the region of the optic thalami has been shown by Freund and others who found that, after section of the cervical cord or after removal of the forebrain and thalami, septic and other materials which ordinarily cause fever in rabbits fail to produce a rise of body temperature.

Clinically, rises of temperature are not uncommon after *cerebral hemorrhages* and particularly after those where blood enters the lateral ventricles. Such hyperthermias are due, in part at least, to mechanical or chemical irritation of the basal portions of the brain where the heat regulatory centers are located. Inasmuch as the temperature of the body is under nervous control, the question naturally arises whether this control can be influenced by the higher nerve centers and particularly whether there exists such a thing as *hysterical fever*. On this point opinions differ. Some deny the existence of hysterical fever while others believe that hysteria may cause the most extraordinary elevations of temperature (41.1° C. (106° F.) and over). One must accept the fact that in hysteria as in other conditions unusual muscular exertion (convulsions) causes slight elevation of temperature and it is possible that in hysteria the temperature regulation may be less perfect, so that such rises may be greater than in health. On the other hand, the excessively high temperatures ascribed to hysteria may well be regarded with suspicion. Many have been proved to be fraudulent, the mercury in the thermometer having been raised by such methods as contact with a hot water bag, etc. Others may have been due to undiagnosed febrile diseases such as tuberculosis, malaria, etc. *Reflex fevers* have also been described, especially after biliary colic, catheterizations, etc., but at least some of these and probably all are due to coincident infection.

Simple Chemical Substances

Fever has been produced in animals, as well as in man, by various chemical substances of a simple character. In children, particularly, but occasionally in adults, the administration of sodium chlorid by mouth has been a cause of fever. When salt solution is injected under the skin or directly into the veins more or less fever not infrequently follows. In some cases this so-called *salt fever* seems to be due to an "unbalanced" salt solution and is prevented by adding calcium and potassium salts in approximately the proportions present in Ringer's solution. It has been shown, however, that the violent febrile reactions which occasionally follow the intravenous injections of considerable quantities of salt solution, and especially solutions of salvarsan, may be almost eliminated if freshly distilled water be used for the injections. The cause of this fever, the so-called *water fever*, seems to lie in the presence of some minute trace of organic matter in the water used for injection rather than in the sodium chlorid or the water itself.

Fever has also been produced by the administration of a variety of *chemical substances.* Among these are caffein and xanthin. Mandel has suggested that in infection the increased purin metabolism may be directly responsible for the increased temperature. Fevers have also been produced in animals by aloin and particularly by tetrahydronaphthylamin. Benedict and Carpenter have reported cases of fever in man which were presumably due to intoxication with the vapors of mercury. The writer has seen fever in man after strychnin poisoning.

Injection of Foreign Protein

Vaughan and his coworkers, as well as many others, have shown that it is possible to produce fever in animals by the repeated injection of foreign proteins. By choosing the proper doses and time intervals one may produce at will continuous, remittent, or intermittent fevers; or by the use of large doses febrile collapse. The proteins used for this purpose are varied. They may be those of egg-white or they may be derived from the bodies of bacteria, from laked corpuscles of a foreign blood, or from other sources. Many cases of so-called *aseptic fever* are due to the destruction of tissues within the body. It seems probable that this tissue destruction liberates proteins which cause a rise of body temperature. In this way the rise seen after severe contusions, fractures, internal hemorrhages, etc., may be explained without assuming that there has been a coincident infection. There seems to be no reason for assuming that the fibrin ferment plays a predominant part in the production of such fevers. Of the fever producing elements in freshly shed blood, the disintegrating platelets seem the most important.

The mechanism by which the parenteral introduction of foreign pro-

teins causes fever is probably the same as the mechanism leading to the various phenomena of anaphylaxis (see Phenomena of Infection). The foreign proteins are disintegrated or cause a disintegration of other proteins in the body and certain products of this change are the immediate cause of the fever. These products act upon the central nervous mechanism which regulates the temperature of the body, for, as we have seen, no fever results when they are injected into an animal after division of the cervical spinal cord or after excision of the midbrain.

Infections

The fever present in infections is probably closely related to that produced by the parenteral injection of foreign proteins. The microörganisms growing within the body liberate a continual supply of foreign protein substances and these probably cause the fever and many phenomena of infection.

No constant relation exists between the severity of the infection and the height of the fever. It is well known that in mild infections the temperature is usually low, whereas in severe infections the temperature is more apt to be high. Yet in the most severe infections of all the temperature may not be very high; indeed, in place of fever we may have a fall in temperature, the so-called febrile collapse. If we regard fever as the expression of a reaction on the part of the body to the infecting organism these varying relations between infection and the height of fever become more clear. Mild infections call forth mild responses and more severe infections call forth more marked responses. In the most severe infections of all, however, or in patients already weak or debilitated, the body fails to make an adequate response to the infectious agent and succumbs without a normal reaction.

The exact cause of the marked fluctuations of the temperature which frequently occur during fever is not well understood. In some this seems to be an exaggeration of the normal diurnal variation with a high temperature in the late afternoon and a low temperature in the early morning. This type of irregular fever, seen particularly in tuberculosis and in the declining stages of typhoid fever, may possibly depend upon the same factors that produce the normal diurnal changes. These, as we have seen, are determined in part by the ingestion of food, by muscular exercise, and by the other activities of the waking day; in part, they depend upon a periodicity which is not entirely interrupted by a change from day to night work. The more irregular variations of febrile temperature and those which do not show an evening rise are not easily explained. Such irregular temperatures occur particularly in malaria, certain cases of sepsis, etc. In malaria the chill coincides with the sporulation of the organisms and it is probably due to the sudden liberation of proteins resulting from the disintegrated corpuscles or from the parasites themselves. Heubner has

shown that the injection of an extremely fine paraffin suspension will cause fever and it is just possible that the malarial paroxysm is due to the mechanical effect of the large number of small bodies in the blood stream rather than to chemical substances.

The Significance of Fever

The relation of the febrile elevation of temperature to its cause, the infection, has always been a problem of great interest on account of the practical question involved: to what extent should one attempt to reduce the temperature during an infectious disease? Up to the time of Liebermeister the opinion generally prevailed that the febrile rise of temperature was on the whole a favorable manifestation and assisted the patient in overcoming the disease. Against this point of view, Liebermeister exerted his great influence and advocated the view that hyperthermia was the essential manifestation of infection, that it was dangerous in itself, and that it should be vigorously combated. Since that time the question of the favorable or unfavorable influence of the increased temperature upon patients suffering from infectious diseases has been under more or less continual discussion.

It is difficult to obtain a satisfactory answer to this question from observations on patients on account of the many factors which must be considered. It is, for example, a common experience that patients with high temperatures are more sick than those with low temperatures. This is probably so, not because the high temperature is itself an unfavorable form of reaction, but because such patients are suffering from more intense infections. Furthermore, as we have seen, in the most unfavorable infections of all the temperature may be low. It becomes difficult, therefore, to estimate the favorable or unfavorable effect of temperature upon infection through a comparison of different clinical cases. Nor does our experience with antipyretic measures give a clear answer to the question, for these measures not only reduce the temperature but they have various effects upon other portions of the body and especially upon the brain and the circulation. The reduced mortality which has followed the bath treatment of typhoid fever, for example, is to be attributed not alone to the reductions of body temperature produced by the baths but to the favorable effect which these produce upon the nervous system and the circulation. The importance of these other effects is evident from the fact that a reduction of temperature produced by the liberal use of antipyretic drugs is not regarded as equivalent in value to a similar reduction produced by hydrotherapeutic measures.

We are indebted, particularly, to experimental studies for our data concerning the relative effects of high temperature and of infection upon the body. It has been shown that moderate hyperthermias without infec-

tion, such as may be produced by exposure to moist heat, are borne by animals without serious consequences. The body temperatures of rabbits have been kept at 41° C. (105.8° F.) and over for weeks at a time without serious damage. The degeneration of the internal organs so often observed in those suffering from infectious processes does not follow such a prolonged overheating of the body. The chief effects produced are an increased body metabolism, a moderate anemia and some loss of weight. Serious effects only result when the body temperature has been raised to heights not usually encountered in fever. It is evident, therefore, that animals endure an increase in the body temperature equal to that which occurs in fever without serious consequences. It is the infection and not the hyperthermia which causes the serious damage to the body in infectious processes.

The question remains, however: does the hyperthermia exert a favorable or an unfavorable effect upon the course of an infection? It is conceivable, for example, that the high temperature might act directly upon the invading organism or that it might assist the infected host in developing its protective mechanisms. The temperatures encountered in fever are sufficiently high to inhibit the growth of certain bacteria. In test tube experiments it has been shown that the gonococcus, the pneumococcus and some others do not grow as well at temperatures of 40° C. (104° F.) and over as at normal body temperatures. It is possible, however, that these experiments cannot be applied to infecting organisms on account of the different conditions of growth in the animal body and in the test tube.

Experiments have also been made to determine the effect that is produced upon the course of an induced infection by artificially raising the temperature of the body. In such experiments the body temperature is raised by placing the animal in a steam cabinet, by puncture of the heat centers at the base of the brain, or by injection of some aseptic pyrogenic material. Experiments of this type have given variable results. Erysipelas has been made milder and shorter by overheating the body; and infections with staphylococcus, pneumococcus, diphtheria bacillus and others have in the hands of some investigators run milder courses when the body temperatures of the animals were artificially elevated. Other observers, however, have not been able to obtain definite results.

Finally, comparative experiments have been made in order to determine with what speed the various protective substances are formed and the amounts that are formed:

(1) When infected animals have been artificially heated, and

(2) When the infections have been allowed to run their natural course.

These experiments have shown in general that with moderate overheating of the body the formation of agglutinins, bacteriolysins and antitoxins is increased. According to Rolly, the favorable effect of higher body temperatures exists up to temperatures of 39.5° C. to 40° C. (103.2°

to 104° F.) while beyond this point the formation of antibodies may be interfered with by the high temperatures.

From the results of studies upon animals, therefore, we must conclude that a moderately high temperature, even though maintained for a long time, is not in itself a dangerous manifestation. On the whole, an increased temperature causes artificial infections in animals to run a more favorable course and it increases the speed with which protective antibodies are formed. Modern studies, therefore, have shown that the high temperatures accompanying infections are up to a certain point a favorable element in the combat against the disease. In the treatment of fevers one should not attempt to force down the high temperatures too vigorously except in cases where they reach unusual heights (41° C. (105.8° F.) or over). In such cases, as in the hyperpyrexia of acute rheumatic fever, the reduction of body temperature may become imperative. Ordinary febrile temperatures do not constitute an absolute indication for active interference. The value of antipyretic measures in such cases is to be judged not solely from their effect in reducing the temperature but also from their effect upon the general condition of the patient and particularly upon his nervous symptoms and the circulation.

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Chapter X

Infection and Immunity

The Conception of Infection

General Considerations

Infection takes place when a foreign organism, by invading and maintaining itself in the tissues of a host, produces the symptoms of disease. Occasionally an invasion is of mutual benefit to the invader and to the host. This is true, for example, of the nitrifying bacteria which live on the root hairs of leguminous plants and which furnish these plants with nitrogenous compounds synthesized from the nitrogen of the air. Such a beneficial symbiosis is also conceivable in the case of man and the higher vertebrates, but no definite instances are known in which an invasion of their tissues by foreign organisms is beneficial in its effects. As a rule, such an invasion is associated with definite evidence of disease, though in a few instances the host seems little harmed by the infection. This is the case, for example, in rats who harbor the trypanosomes of Lewis in their blood, and in certain human infections with filaria.

Invasion of the host is obviously present when the infecting organisms can be demonstrated in the blood stream or the living tissues. It is not present when the organisms simply lie on a surface of the body. Healthy individuals commonly harbor staphylococci in the skin, the Bacillus xerosis in the conjunctival sac, cocci and spirilli in the mouth, colon and other bacilli in the intestines, and Döderlein's bacillus in the vagina. Many of these organisms are capable of producing disease if they enter the body under favoring conditions. Ordinarily, however, the epithelial coverings of the body resist their penetration into the tissues, and so long as this resistance is effective no invasion and no infection takes place.

Bacterial Intoxication.—For a true infection to occur it is necessary that the foreign organisms invade the living tissues of the host. Diseases that result from the absorption of toxic bacterial products formed outside of the body are not infectious. Thus the Bacillus botulinus forms a poison outside of the body by its action on meat, beans, etc., and the disease

produced by the absorption of this poison is a bacterial intoxication rather than a true infection. In other cases the distinction between bacterial infection and bacterial intoxication is less clear. For example, when bacteria grow in necrotic tissues, symptoms may be produced by an absorption of the soluble products of tissue decomposition or bacterial growth. Strictly speaking, such symptoms are due to an intoxication rather than to an infection, so long as the organisms present do not invade the living tissues. Certain bacteria, such as the diphtheria and tetanus bacilli, form soluble poisons, and the characteristic manifestations of the diseases to which they give rise are due largely to the specific action of these poisons. Such poisons are not formed by the great majority of infectious agents, so that in each of these diseases we are dealing in part with a specific bacterial intoxication. However, since these intoxications commonly take place only when the bacteria are able to maintain themselves within the tissues of the host, the intoxication is usually a result of infection.

Local and General Infections

Localized Infections

When organisms gain entrance to the body and are not immediately killed, the defenses at the point of entrance may be sufficiently active to limit the growth of the invaders to a restricted zone. This results in a local infection at the point of invasion. The conflict between host and invader usually gives rise to a local inflammation, the severity of which is determined by the degree of conflict between the two forces. Localization at the point of invasion is, however, a relative term, for the degree of localization may vary from that seen in a superficial boil to that seen in the spreading phlegmon of a streptococcus infection. In strictly local infections, organisms that escape into the blood or lymph streams are promptly killed, and are not allowed to establish themselves in distant parts of the body.

Secondary Localizations.—When invading organisms escape into distant parts of the body without being promptly killed, the infection is no longer localized to the point of invasion. Not infrequently the invaders settle and multiply in definite regions. These secondary points of infection are determined in part by the character of the invading organisms, and in part by the conditions of local tissue resistance. Thus the virus of rabies and that of poliomyelitis seem to concentrate particularly in the central nervous system, gonococci and certain types of streptococci tend to settle in the joint and on the heart valves, glanders bacilli injected into the peritoneal cavity of the male guinea-pig lead to an infection of the testicles, etc. Injury to the tissues may also determine the point at which invading organisms localize. For example, staphylococci tend to produce

osteomyelitis in bones that have been the seat of injury. In many such metastatic infections there is little or no reaction at the point of entrance to the body, and this point may indeed be determined only with great difficulty. Having localized at one or more secondary foci, the infection may then proceed with the clinical manifestations of a strictly local disease, as happens, for example, in osteomyelitis. It is evident from the nature of secondary localizations, however, that a wide distribution in the body must often occur, and that no sharp line separates the severe cases from generalized infections. If the secondary localizations are numerous and give rise to abscesses, the condition is spoken of as a pyemia.

Septicemia

True Septicemia.—When bacteria can be recovered from the blood stream a bacteriemia or septicemia is present. Bacteriemias are of two types, and within each type there are various grades of severity. The first type, which constitutes a septicemia in the strict sense of the term, is characterized by the growth and multiplication of the infecting organisms in the circulating blood. Such a true septicemia may be produced experimentally by injecting highly virulent organisms, such as anthrax or plague bacilli, into very susceptible animals. It seems probable that in man a growth of bacteria in the blood stream is not necessarily so serious as might be expected from the examples of septicemia that have been produced experimentally in animals. During the early stages of typhoid fever, for example, bacilli are regularly present in the blood stream, and they probably multiply there; yet the septicemia, in this instance, is not of exceptionally grave import.

Septicemia from Local Foci of Infection.—In the second type of septicemia the bacteria enter the blood, more or less continuously, from some local area of infection. They are, however, unable to maintain themselves in the blood, but are being constantly destroyed by the specific immune substances which are present in the body fluids. The organisms present in the blood are, therefore, merely transients that have escaped from local foci. Among the bacteriemias associated with the local foci of infection, the most important are those of malignant endocarditis and septic venous thrombosis. The relation between the bacteriemia and the local disease is particularly evident in the septic venous thrombosis that not infrequently complicates mastoid disease. That the bacteria in this instance are derived from the local focus of infection, and are often unable to maintain themselves continuously in the blood, has been demonstrated repeatedly, for the bacteriemia usually disappears when the diseased veins are ligated and drained.

Differences between the Two Types.—It is evident that such a secondary bacteriemia is fundamentally different from the type which results from a free growth of organisms in the blood stream itself. In the

latter, the body fluids are unable to cope with the invading organisms. In the former, the body fluids may be able to destroy such invaders as escape from the foci of infection and the immune substances in the body fluids may be markedly increased. Within the local foci, however, the invaders are more or less protected from the action of these antibodies and from these foci the invaders enter the blood or lymph streams more or less continuously. Such an entrance is particularly easy when the foci are located within the blood vessels or on the heart valves. From the therapeutic standpoint, also, the distinction between a true septicemia and one secondary to foci of infection is fundamental. In the former, one may perhaps endeavor to destroy the organism circulating in the blood. In the latter, the blood is not the real seat of the disease, and its bactericidal properties are often high. Therapeutic efforts should be directed more particularly toward a removal or cure of the primary focus or foci of infection, particularly by surgical methods. If these foci can be destroyed, the bacteriemia will often be overcome by the defensive mechanisms of the body fluids.

Acute and Chronic Infections

An infection, whether general or local, may run either a rapid or a prolonged course. An acute course indicates a lively conflict between the host and the invader which results in a decisive victory for the one or the other. If the invader is entirely overcome, the host recovers; if the invader is wholly victorious, death ensues.

Chronicity results when, for any reason, neither the host nor the invader is able to gain a decisive victory. The invading microörganisms establish themselves within the tissues of the host and are not expelled. At the same time the host does not succumb to the infection. Chronicity may be due to various causes. It may result from the focal character of the infection. The general defenses of the body may be excellent, and bacteria which escape into the blood may be promptly killed. Nevertheless, the local conditions about the infection may be such that the invader is protected from direct attack by the host, and within the focus of infection it may grow and multiply. Again, a disease may be chronic because neither the host nor invader is able to muster sufficient offensive properties to overcome the defense of the other. The defensive properties of each may be relatively marked, the offensive relatively weak. During the course of an infection both host and invader may develop a considerable resistance to the offense of the other, so that the disease passes gradually into a subacute and chronic stage. Finally, as Theobald Smith has pointed out, there is another type of parasite which may dispense largely with both offensive and defensive properties. We may conceive of this type as exerting a metabolic activity approximating so closely to that of the host that

the latter reacts but slightly, and then only after a long period of stimulation. This type of parasite would have very little that is body-foreign or blood-foreign. In this class he places the spirochetes of syphilis.

The Portals of Entry

The phenomena of infection and of immunity may be regarded as manifestations or results of the conflict between two contending organisms, the host and the invaders. In this conflict the invaders must first effect an entrance to the body of the host. After this has been accomplished, the ensuing history depends in part upon the invaders' ability to maintain themselves against the attacks of the host, and in part upon the invaders' offensive properties and the ability of the host to defend himself against these. The countless variations seen in the course of the infectious diseases are due to the numerous variations in each of these individual factors. Each disease, and to a certain extent each individual infection, presents separate problems. Broad generalizations as to the offensive and defensive properties of host and invaders, as well as to the modifications of these properties during the course of the various infectious diseases, are not possible.

First Step in Infection.—The first step in every infection consists in the entrance of the foreign microörganisms into the tissues of the host. This entrance may be effected in various ways and at various parts of the body, and the mode of entrance plays no small part in the subsequent history of the infection. A knowledge of the mode of infection is of the greatest importance in the prevention of infectious diseases.

The point at which the infection enters is spoken of as the portal of infection, and we shall, therefore, consider first the more common portals of infection and the conditions which govern the entrance of microörganisms at these various portals.

The Skin

As a general rule, the unbroken skin affords an efficient protection against invasion by the various bacteria with which man comes in contact. Only exceptionally do infections take place through a normal skin. The best example of such an infection is the production of boils by rubbing pure cultures of virulent staphylococci into the unbroken skin. Plague bacilli may be introduced into guinea-pigs by placing infectious material on the carefully shaved surface of the skin, but in this case it seems probable that the bacteria penetrate the skin through slight abrasions produced by the shaving. Various animal parasites may burrow into the skin, and infections with hookworm are usually due to a penetration of the unbroken

skin by the larvae of the worms. The symptoms of "ground itch" are due to this manner of gaining entrance to the body.

Infection through Broken Skin.—The great majority of infections through the skin take place through some break in its continuity. This break may be so small as to escape a cursory examination. Infection is also favored by a local injury at the point of entrance, for the injured tissues and the local extravasation offer a more favorable opportunity for the growth of the invaders. This is particularly true of infections with tetanus bacilli. Punctured or contused wounds are much more liable to tetanus infection than are clean-cut wounds, and a few tetanus spores free of toxin may be placed in a clean wound without causing the disease. Tetanus is also favored by the presence of pyogenic organisms, possibly because these injure the tissues, and possibly because they create the more strictly anaërobic conditions necessary for the growth of tetanus bacilli.

Of the numerous infections that may gain entrance to the body through the broken skin, we may mention infections with the pus cocci, rabies, anthrax, tetanus, syphilis, plague, etc. Infections with plague are of particular interest, for the reason that such infections frequently result from the bites of infected fleas. Plague is primarily a disease of rats and other rodents, and fleas commonly acquire the bacilli from having bitten infected animals. It is probable that the flea neither suffers from a plague infection nor directly inoculates man during its feeding; but that the bacilli live in its digestive tract, pass out with its dejecta in a live and virulent condition, and, being deposited in the neighborhood of the bite, subsequently penetrate the abraded skin, particularly if the individual rub or scratch the region of the bite.

From Bite of Blood-sucking Parasite.—Various other infectious diseases are transmitted by the bites of blood-sucking parasites. In some cases, as in that of plague, the parasite appears to be simply a carrier of the infectious agent. In other cases, the infecting organism undergoes a cycle of development within the parasite, and until this cycle is completed infection does not follow its bite. The malarial organism, for example, must complete its sexual cycle of development in the Anopheles mosquito before the latter can transmit the disease to man. Similarly, yellow fever is transmitted by the Stegomyia mosquito only after a definite period of incubation. Among other diseases conveyed by the bites of animal parasites are typhus fever, transmitted by the body louse; Rocky Mountain fever, transmitted by the tick; and dengue fever and filariasis, which are probably transmitted by mosquitoes.

Mucous Membranes Near Body Surface

The mucous membranes near the exterior of the body are exposed to a great number and variety of microörganisms. Their resistance to invasion, though considerable, is not equal to that of the skin. The con-

junctivae, even when intact, may become infected by various bacteria, among which are gonococci, pneumococci and diphtheria bacilli. The mucous membrane of the nose is a common site of infection in acute coryza. The unbroken mucous membrane of the mouth is very resistant to the penetration of microörganisms. About the teeth, however, infections are not infrequent, and chronic infections near their roots are believed to be an important cause of the low grade sepsis present in many cases of chronic arthritis.

Vulnerability of Tonsils.—The tonsils constitute the most vulnerable portion of the upper respiratory and digestive passages. Owing to the anatomical structure of the tonsillar crypts, microörganisms readily lodge in them, where these organisms may grow and multiply. The mucous membrane lining the crypts is frequently damaged, and an opportunity is thus afforded for the penetration of bacteria into the substance of the gland and from here into other parts of the body. Infections of the tonsils are frequently produced by streptococci and other cocci, by the organisms of Vincent's angina and by diphtheria bacilli. The tonsils may also be the portals of entry for tuberculosis, syphilis and other diseases. Local foci of infection in the tonsils may be the source of acute or chronic sepsis; and the intimate relationship between tonsillar disease, on the one hand, and arthritis, endocarditis and nephritis, on the other, has been repeatedly emphasized in recent years. Removal of the tonsils from such patients may check a low grade sepsis, or it may guard the patient from future bacterial invasions from this source.

Urethra.—The urethra is the common site of gonococcus infections. No primary abrasion of the mucous membrane seems necessary for the establishment of this infection.

The Gastro-intestinal Canal

The stomach is rarely the site of a bacterial invasion. Furthermore, the acid gastric juice possesses some antiseptic power, and this affords some protection to the intestines against infection by pathogenic organisms that may be swallowed with the food or drink. This protection is not very perfect, however, even in healthy individuals, for a part of the food and most of the water swallowed normally pass promptly through the pylorus into the duodenum (page 151). When the stomach empties itself prematurely or when the gastric secretion contains little or no acid, unusual quantities of undigested and undisinfected food may enter the intestines. Intestinal disturbances are indeed not uncommon in patients with gastric achlorhydria, and these disturbances are due in part to abnormal bacterial activities, which are favored by lack of gastric digestion and disinfection.

Infections Entering by Intestines.—The intestines constitute the usual

portal of entry for a variety of infections. Among these are typhoid and paratyphoid fever, dysentery and cholera. Tubercle bacilli may also enter the body through the digestive tract. In the case of cholera the infection usually remains localized to the intestinal mucous membrane, whereas in typhoid and paratyphoid fevers the infection early takes the form of a general bacteriemia. Tubercle bacilli may pass through an apparently intact mucous membrane without causing a demonstrable local lesion at the point of penetration. The regional lymphatic glands may become diseased, or the tubercle bacilli may pass these and involve other and more distant parts of the body.

The Respiratory Passages

The lungs are protected from bacterial invasion by a number of special mechanisms (page 391). Particles floating in the inspired air are caught by the mucus that covers the upper respiratory passages and those that lodge in the trachea and larger bronchi are propelled toward the larynx by the cilia that line these passages. Coughing and sneezing serve to expel foreign bodies and collections of mucus.

Infections of Respiratory Tract.—Infections of the respiratory tract are caused most commonly by pneumococci, streptococci, influenza bacilli or tubercle bacilli. Acute infections frequently start in the upper respiratory passages and gradually extend downward. A coryza and pharyngitis is not infrequently followed by a bronchitis, and this in turn may precede the onset of pneumonia. According to Cole, about 50 per cent of patients with pneumonia give a previous history of inflammation of the upper respiratory passages. Pneumonia has also been produced experimentally by the injection of pure bacterial cultures into the bronchi.

Tuberculosis.—Tubercle bacilli enter the body by various paths. We have already pointed out that they may be inoculated through the broken skin, that they may pass through the apparently intact mucous membrane of the intestines, and that they may invade the tonsils. From the last two localities particularly an invasion of the lymphatic channels, with subsequent involvement of the lungs, may take place, and some have maintained that these are, indeed, the most frequent portals of entry in the usual type of pulmonary tuberculosis. According to this view, tubercle bacilli which are inhaled rarely infect the lungs or air passages directly, but only after they have been swallowed or have penetrated the tissues of the tonsils. While these paths of infection cannot be denied, nevertheless it seems probable that they are not the usual paths of infection in the pulmonary tuberculosis of adults. The more common path is probably the direct infection of the lungs or air passages by bacilli suspended in the inspired air. The experience of pathological anatomists favors this view, as do also the experiments which showed that while a small number of

bacilli may cause tuberculosis when inhaled, much larger quantities are required to produce the disease when ingested.

Defensive Properties of Infectious Microörganisms

We have seen that microörganisms cause infection only when they are able to maintain themselves in the fluids or tissues of the host. In order to do this they must withstand the attacks to which they are subjected. These attacks probably vary in intensity; and while some invaders call forth but little response on the part of the host, others call forth a violent reaction. The ability of a foreign microörganism to defend itself against these attacks constitutes one of the important factors in what is known as its virulence.

Virulence

The virulence of microörganisms varies greatly not only among different strains, but also in the same strain at different times and under different circumstances. The study of factors that reduce the virulence of pathogenic microörganisms has assumed great importance in the preparation of living cultures for use as prophylactic vaccines against disease. As a general rule, cultivation on artificial media tends to reduce virulence, particularly when the growths are exposed to unusually high temperatures, to injurious chemicals, or to the products of growth of the microörganism itself. On the other hand, the passage of microörganisms through the bodies of susceptible animals tends to increase their virulence. Certain bacteria, such as Friedländer's bacillus, maintain a relatively constant virulence under varying external conditions. Others, such as the streptococci, change their virulence quickly and markedly when the conditions under which they are kept or grown are varied.

Specific Virulence for Certain Animals.—The increase of virulence caused by the passage through the bodies of susceptible animals was utilized by Pasteur in the preparation of his fixed virus for the treatment of rabies. When the virus from a mad dog is inoculated into rabbits the resulting disease develops in from 14 to 21 days. If the virus be successively inoculated from one rabbit to another, the incubation period shortens until finally the rabbits invariably sicken on the sixth or seventh day and die on the ninth or tenth day. Of great importance is the fact that this increased virulence is specific for rabbits. With each successive passage through these animals the virulence of the virus for dogs diminishes. Similarly, the passage of the rabies virus through monkeys may reduce its virulence for rabbits almost to extinction. Furthermore, Pasteur found that when the bacilli of swine plague were passed through rabbits or pigeons the virulence for these animals increased, but at the same time the

virulence for hogs diminished. Streptococci may also show an increased virulence for one animal while losing some of their virulence for another. It is evident, therefore, that the virulence of a microörganism is a quality which may be more or less specific for a given species of animal.

Increased Resistance to Certain Drugs.—This development of resistance to deleterious influence is not limited to an increased defense against the attack of a particular host, but it may also show itself against poisons of a relatively simple composition. Thus anthrax bacilli can be accustomed to increasing strengths of arsenic. When patients having trypanosome infections are treated with arsenic compounds, trypan red, or other drugs, a large number of the infecting organisms may be killed. On the other hand, the organisms left in the body may give rise to a strain which is particularly resistant to the drug used. The spirochetes of syphilis are said to become more resistant to salvarsan, and certain strains of malarial parasite seem to become relatively resistant to quinin. Apparently in such cases we are dealing with a survival of the fittest. The organisms which resisted the original doses of the drug used give rise to a race of resistant descendants.

Morphological Changes in Virulent Bacteria.—In some instances the phenomenon of resistance to destruction and of increased virulence is associated with well-defined morphological changes in the microörganisms. It has been observed, for example, that bacteria, like plague bacilli, pneumococci and certain streptococci, are more virulent when in the capsulated stage. As the organisms are passed through animals an increase in capsule formation and an increase in virulence go hand in hand. When grown in artificial media the loss of capsules and the loss in virulence occur simultaneously. Other organisms which do not form capsules seem to develop changes in their ectoplasm coincident with changes in infecting properties. It has been noted, for example, that colon bacilli appear larger when recovered from fatal infections of guinea-pigs, and the same is said to be true of streptococci. Apparently this thickening is due to the changes in the exterior layer of the bacteria, which renders them less vulnerable to the attacks of the host.

Specific Defensive Mechanism.—It is evident, however, that the changes whereby a pathogenic organism increases its virulence for one species of animals while losing its virulence for another, cannot be explained in so simple a way as by a change in its ectodermic covering. Welch has pointed out that bacteria, like their hosts, probably acquire a specific defensive mechanism which enables them to resist the attacks of the host. Bacteria which have been cultivated on the sera of immunized animals may show an increased resistance against the bacteriolytic and agglutinative substances of immune sera. According to Rosenow, there is a definite relationship between the virulence of pneumococci and their resistance to phagocytosis, and he was able to extract substances from

virulent pneumococci which inhibited the action of pneumococcus opsonin (page 535). It is readily conceivable that this resistance to bacteriolysis or phagocytosis should be more or less specific against the antibodies furnished by a particular species of animals.

Offensive Properties of Infectious Microörganisms

The defensive properties of infectious microörganisms enable them to resist the attacks of the host, and thus permit their multiplication within the tissues of the latter. In addition, infecting microörganisms do harm to the host by virtue of their offensive properties.

Ptomains

When it was discovered that basic nitrogenous compounds, known as ptomains, were found during the putrefaction of organic matter, and that certain of these ptomains were toxic, it was surmised that these same organic bases might be formed during infections, and that they might be responsible for the toxic symptoms observed during the infectious diseases. Further studies have shown, however, that such substances are not formed in appreciable quantities during the course of the infectious diseases, and that they are probably not responsible for the toxic symptoms observed. The pathological importance of ptomains seems limited to the possibility that, when decomposed food is eaten, toxic symptoms may be produced by poisonous ptomains formed in the decomposed food. Such intoxications, however, have little in common with the infectious diseases. Furthermore, the great majority of disorders which have resulted from the ingestion of decomposed food have been due, not to the presence of ptomains in the food, but to infections from pathogenic bacteria that were swallowed with the food.

Soluble Toxins

Soluble toxic substances are elaborated by the diphtheria bacillus, the tetanus bacillus and certain other bacteria. If such bacteria are grown under proper conditions the toxic substances pass into the culture fluids, and may thus be separated from the bacteria themselves. When injected into animals these soluble toxins may produce much the same symptoms as do the diseases themselves. The symptoms of these diseases are, therefore, due in large part to the action of the soluble toxins secreted by the bacilli during their growth in the infected animal. The exact composition of bacterial toxins has not been determined. It has been impossible thus far to separate them entirely from proteins. Such toxins are responsible for many symptoms produced by the diphtheria bacillus and the tetanus bacillus. They are also formed by the Bacillus botulinus, the Bacillus

pyocyaneus and the Bacillus of symptomatic anthrax. Biologically such soluble toxins are characterized by the fact that, in common with the vegetable poisons ricin and abrin, certain snake venoms, and the ferments, they give rise to the production of neutralizing antitoxins when they are injected into the animal body.

Endotoxins

The vast majority of infectious microörganisms, and notably the typhoid bacillus, the plague bacillus and the cholera spirillum, produce no soluble toxins. Filtrates from fresh and actively growing cultures do not give rise to the characteristic symptoms of the diseases produced by the living organisms. Nor do these filtrates give rise to protective antitoxins. When the organisms have been allowed to disintegrate, however, or when the dead bodies of the bacteria are injected, certain toxic symptoms may be produced. On the basis of such experiments it has been assumed that these bacteria contain within their bodies certain poisons, the so-called "endotoxins," which are insoluble and which are liberated only when the bacteria themselves disintegrate. The symptoms of the infectious diseases produced by such microörganisms are believed by some to be due to the liberation of the toxic "endotoxins" from the bodies of bacteria destroyed in the host during the course of the disease. According to this view, each pathogenic organism possesses certain definite endotoxins, and the specific character of an infection is due to the specific character of this poison which is liberated in the body of the host in consequence of bacterial disintegration.

Non-specific Protein Poisons

Opposed to this view of the specific character of the insoluble "endotoxins" in different bacteria is the view of Vaughan and of Friedberger, that, in infectious diseases of this type, we are dealing not with specific bacterial poisons, but with an intoxication which is analogous to that produced by the disintegration of any foreign protein within the animal body. Vaughan has shown, for example, that many phenomena of infection may be reproduced by the parenteral injection of various kinds of foreign protein. He believes that these phenomena are not determined by specific bacterial endotoxins. The question will be discussed more fully when the phenomena of anaphylaxis are considered (page 536).

Immunity, Resistance and Susceptibility

In the preceding paragraphs infection has been discussed chiefly from the standpoint of the invader. An equally important rôle, however, is played by the host. When a given number of microörganisms of definite

virulence are introduced into an animal, they may produce no disease whatsoever. The animal is said to be immune. They may, on the other hand, produce a mild disease with recovery, or a severe disease resulting in death. The animal is then said to be susceptible to the infection to a lesser or greater degree. All such reactions depend to some extent upon the dose, the virulence, and manner of introducing the infectious agent. Some animals succumb to exceedingly minute doses, while others require very large doses, or may, indeed, resist all attempts to cause infection. Furthermore, microörganisms which cause death when injected into an animal may be relatively harmless in a state of nature, for the reason that they are unable to gain entrance to the body in sufficient numbers to cause infection.

Immunity to infection may be natural to the host; it may be acquired by having passed through the disease in question, or it may be produced by injecting specific protective substances.

Natural Immunity

Wide variations exist among different species of animals in their susceptibility to different diseases. Many infections that afflict man, for example, do not occur naturally among animals. Among these are influenza, typhoid fever, cholera, gonorrhea, syphilis, yellow fever, malaria, and the acute exanthemata. Some of these diseases have not been transmitted to the lower animals; some are transmitted only with difficulty and to species closely related to man, while the organisms that cause still others are pathogenic to certain animals, but do not reproduce a disease which resembles clinically that which occurs in man. On the other hand, many diseases that occur among animals are not transmissible to man. Different species of animals, therefore, are susceptible to different infectious diseases; or, conversely, immunity to certain infections is a characteristic of the species to which an animal belongs.

Cause of Immunity in Different Species.—The cause of these differences among species is but imperfectly understood. In a few instances they seem to depend upon differences in body temperature. Thus frogs, which are ordinarily resistant to anthrax, may be infected if they are kept at temperatures of 35° C.; and lizards, which are resistant to plague bacilli, may be infected if the temperature of the surrounding air is raised. The bacilli of avian tuberculosis grow best at temperatures of 40° to 45° C., while the bacilli of mammalian tuberculosis cease to grow at temperatures above 40° C. Since the body temperature of birds is considerably higher than that of mammals, the different susceptibility of these animals to the different strains of tubercle bacilli may be explainable in part by the differences in the body temperatures. It has been suggested also that differences between herbivora and carnivora may depend upon the differ-

ence in their food supply. As a rule, however, the wide differences in susceptibility to infection exhibited by different species cannot be explained so simply. As we shall see, biological reactions of various kinds have demonstrated that marked differences exist in the proteins of different species of animals, and it seems probable that the observed differences in natural immunity are but another expression of these biological differences among different species of animals.

Varying Susceptibility of Different Races.—Different races belonging to the same species may also show variations in susceptibility to certain infectious diseases. For example, Algerian sheep are relatively immune to anthrax, whereas European sheep are quite susceptible. Similarly, gray mice are said to be more resistant to streptococci and pneumococci than are white mice. In man also racial differences have frequently been noted; but it is not altogether certain that these depend upon fundamental differences in racial susceptibility. The high incidence of tuberculosis among the American negroes, for example, depends, in part at least, upon the unhygienic conditions under which they live and the unusual exposure to tuberculosis to which they are subjected. The relative immunity of the black to yellow fever may possibly depend upon less frequent bites by the infecting mosquitoes. The immunity of the natives of Central Africa to malaria is not a natural immunity, but is one acquired by having had the disease in very early life. Some have, therefore, doubted the existence of racial differences in susceptibility.

Infectious Disease Virulent in First Outbreak.—When an infectious disease is introduced for the first time among a race which has never been exposed to the disease previously, it is often particularly virulent in its manifestations. Such has been the history of measles, syphilis, tuberculosis and other infections. In such cases, at least, there appears to be a distinct racial susceptibility to the disease in question. This depends upon the previous freedom from this infection. Whether the relative resistance possessed by races long exposed to the infection is inherited from ancestors who have had the disease, or whether it depends upon a natural selection through the survival of those who could resist, has not been definitely settled.

Individual Susceptibility.—Local Factors.—When a given infectious disease invades a community, only a certain proportion of those exposed become sick. This is doubtlessly due in part to variations in the number of infectious organisms that happen to come in contact with exposed individuals, and in part to local points of lessened resistance which permit a more ready entrance of the infectious agent. For example, catarrhal conditions of the upper respiratory passage predispose to infections by the bacteria causing diphtheria, pneumonia, etc., and catarrhal disturbances of the intestines are said to predispose to cholera. An absence of hydrochloric acid in the gastric juice and an unusually rapid discharge of

the gastric contents into the duodenum permit a more ready access of living cholera or typhoid bacilli to the intestines. Injuries of any kind may permit the entrance of bacteria which would otherwise be resisted, as happens in traumatic pneumonia and many other conditions.

General Factors.—Individual susceptibility to various infectious diseases may also depend upon general factors, such as poor nutrition, fatigue or chilling. This is supported not only by clinical but by experimental evidence. Animals ordinarily immune to a given infection have been made susceptible by starvation, by fatigue from prolonged exercise and by exposure to very high or very low temperatures. The administration of alcohol, clinically as well as experimentally, reduces the resistance to certain infections. Chronic diseases in general render the individual more susceptible to infections. In diabetes, for example, the patients are peculiarly prone to boils and other staphylococcus infections as well as to tuberculosis. Increased susceptibility in such cases depends upon a reduction in certain protective substances in the body (page 290). The fact that patients with chronic diseases frequently die of acute infections has led to the expression that in such cases they do not die of the disease from which they have been suffering.

Naturally Acquired Immunity

It has long been known that a single attack of certain infectious diseases protects the individual from subsequent attacks. Among the diseases which confer such an immunity may be mentioned the acute exanthemata, plague, typhoid, cholera, yellow fever, diphtheria, typhus, and mumps. A single attack of any of these diseases usually endows the individual with a substantial immunity which is lifelong, and second attacks are rare. Other infections ordinarily leave behind no lasting and effective immunity to the disease in question. Repeated attacks of boils, erysipelas, pneumonia, gonorrhea, and malaria are common. Indeed, it has been held that some of these infections, and particularly boils, erysipelas, and pneumonia, may leave behind an increased susceptibility to future attacks. It seems more probable, however, that these infections increase the resistance only for a short time, and that the repetition of attacks is due to other causes, such as a natural susceptibility on the part of the individual, damage to certain tissues or some chronic source of infection. Repeated attacks of erysipelas, for example, may arise from a chronic streptococcus infection in the nose or nasal sinuses.

Immunity to Tuberculosis and Malaria.—Even such infections as malaria and tuberculosis are followed by a certain degree of immunity. Natives born in the tropics owe their resistance to malarial infections in part to early infections with the disease. Mild tuberculosis infections

may protect a guinea-pig from fresh infections. According to Theobald Smith, "the researches of the past twenty-five years have shown definitely that all parasites, from the ultramicroscopic forms to the higher entozoa, induce in the body of the host a degree of antagonism higher than that existing before invasion. This antagonism may not be sufficient to eliminate the parasites; it may not even be strong enough to check the march of the invasion and the progressive disease resulting therefrom; it may even, in some of its stages, be injurious to the host, as when it leads to the hypersensitiveness of anaphylaxis. This increased antagonism exists, however insignificant it seems to us."

Immunity from Unrecognized Infections.—We have seen that immunity may be a characteristic of the species, the race or the individual, or that it may be acquired by having passed through the disease in question. While the theoretical difference between these two forms of immunity is fundamental, nevertheless it is not always simple in practice to distinguish an immunity that is natural to the individual from one that has been acquired as the result of an infection. We know that infections may be of such a mild character as to cause no easily recognized clinical symptoms and that such infections may profoundly alter the reaction of the individual to the diseases in question. For example, 35 per cent or more of all adults react to tuberculin. This indicates the prevalence of this infection in a form that is not recognized clinically but which nevertheless alters the biological reactions of the individual. The importance of such mild and unrecognized infections as an important factor in the spread of infectious diseases is well known, but their rôle in protecting a certain number of individuals against infectious diseases is only beginning to be recognized. Evidence is accumulating that such conditions prevail with respect to other infections than tuberculosis.

Schick Diphtheria Reaction.—Susceptibility to diphtheria may now be tested by means of the so-called Schick reaction. In performing this test an amount of diphtheria toxin equal to one-fiftieth of the minimum lethal dose for a guinea-pig weighing about 250 grams is injected into the human skin. If this injection produces no local reaction, the blood is found to contain at least one-thirtieth unit of diphtheria antitoxin per cubic centimeter, and such an individual seldom acquires the disease. If, on the other hand, the injection produces a skin reaction, the antitoxin content of the blood is less than one-thirtieth unit per c.c., and the individual is relatively susceptible to diphtheria. The practical value of such a test in separating susceptible from relatively immune individuals has led to its wide application by Schick, by Park and his associates, by Kolmer and Moshage, and by others. The results obtained in testing normal individuals are shown in the following table:

Percentages of Persons Susceptible to Diphtheria as Indicated by the Schick Reaction

Arranged According to Age

Age	Schick	Park	Kolmer
Under 1	7	40	12
1–5	53	65.9	54.5
5–10	50	42.5	57.8
10–15	50	26	24
Over 15	50	33	35

As is evident from this table, the Schick reaction indicates that susceptibility to diphtheria is most common between the ages of one and fifteen years, while very young infants as well as adults are relatively immune to the disease. The immunity of very young infants is probably comparable to the immunity which such infants enjoy against various other acute infectious diseases, and is probably transmitted from the mother. The cause of the relative immunity among those over fifteen years is not known, but it may possibly represent an immunity acquired from having had a very mild and unrecognized diphtheria at some previous time.

Skin Test for Typhoid Immunity.—Gay and Force have recently described a skin reaction which in their opinion indicates immunity from typhoid fever. Of twenty-one individuals who had recovered from the disease, twenty gave a positive reaction even after long periods of time. The test was also positive in a large proportion of those who had been recently vaccinated against the disease. On the other hand, 9 per cent of supposedly normal individuals gave positive tests, presumably because at some previous time they had overcome an unrecognized infection with the typhoid bacillus.

Unrecognized Syphilitic Infection.—Serological as well as pathological studies have also shown that a certain number of individuals have had syphilitic infections without history or evident clinical manifestations. The immunity of the nursing mother against infection from her syphilitic child (Colles' law) has in this way been shown to be due to the fact that such mothers already have syphilis, even though the history of infection as well as the physical examination may be negative.

Artificially Acquired Immunity

(a) *Active Immunity*

The observation that a more or less perfect immunity follows certain of the infectious diseases early lead to attempts to immunize by inoculating these diseases into healthy individuals.

Smallpox Inoculation.—Inoculation against smallpox was practiced

by the ancients in China and India, and was introduced into England by Lady Mary Wortley Montague in the early part of the eighteenth century. Inoculated smallpox was far less fatal than the naturally acquired disease, possibly because the average healthy person is better able to withstand infection than one who acquires the disease naturally, possibly because the mode of infection influenced its virulence. Nevertheless, the inoculation of smallpox was not without danger and it was justified at that time only by the fact that relatively few escaped the natural disease.

Vaccination.—The discovery of vaccination by Jenner introduced a new era in the history of artificially acquired immunity. Cowpox, which furnished the material for Jenner's method of vaccination, is now believed to be an attenuated form of smallpox. The dangers of vaccination with cowpox are insignificant, while the protection against smallpox conferred by this means lasts for years.

Injection of Attenuated Cultures.—It remained for Pasteur, however, to apply in a systematic manner the principles involved in vaccination. He found that cultures of chicken cholera bacilli which had been allowed to stand for months decreased in virulence, but that the injection of such cultures into fowls protected them against subsequent infection. Pasteur followed this by a method of preventative inoculation against anthrax, in which the virulence of the bacilli had been attenuated by cultivation at high temperatures (42°-43°). His work along these lines finally culminated in the development of his inoculation treatment for rabies. Various methods for the attenuation of living cultures have been used. Among these are the passage through other animals, growth at high temperatures, drying, and the exposure to chemicals or to the products of bacterial growth.

Injection of Virulent Cultures.—In contradistinction to immunization with attenuated cultures of living microörganisms, attempts have also been made to immunize by introducing into the body very small numbers of fully virulent bacteria and by gradually increasing the number used. By this method Webb, Williams and Barber have succeeded in immunizing against small amounts of fully virulent cultures of tubercle and of anthrax bacilli.

Danger in Use of Living Cultures.—It is evident that when living organisms are introduced into the body the conditions approach those which prevail during an actual infection, and particularly is this true when small doses of virulent, rather than large doses of attenuated, organisms are used. The immunity obtained by these methods is the most reliable that can be produced experimentally. On the other hand, the method is difficult to control so that it will be free of danger. When used on animals an occasional death does not greatly impair its usefulness, provided adequate protection is conferred on the great majority of those inoculated. When used on man, however, the mere possibility of a fatal accident

constitutes a very serious obstacle, and it would then be justified only in the presence of a widespread and fatal epidemic. For man, the living virus has found its greatest applications in vaccination against smallpox and in the treatment of those bitten by rabid dogs. An extensive and effective use of attenuated living vaccines as a prophylactic against cholera has been made by Haffkine. Strong has also recommended the use of attenuated living cultures as a prophylactic vaccine against plague. It is quite probable, however, that in these cases satisfactory results may be obtained by using dead vaccines rather than living organisms.

Injection of Toxins.—The practical difficulties attending the use of living cultures and the danger of occasional accidents from their administration tend to restrict their general application as immunizing agents against the infectious diseases of man. It is simpler and safer, where possible, to produce immunity by methods in which no living organisms are injected. In those cases in which the microörganisms produce a soluble toxin that causes the symptoms of the disease (diphtheria, tetanus, etc.), the injection of this toxin gives rise to an immunity which depends upon the formation of an antitoxin in the body. The production of such an antitoxic immunity in animals is now widely used in the commercial preparation of antitoxins for diphtheria and tetanus. Active immunization of human beings against diphtheria toxin has also been used to some extent as a prophylactic measure against the disease.

Injection of Dead Cultures.—In most instances, however, infecting microörganisms produce no soluble toxin, and the naturally acquired immunity does not depend upon the presence of antitoxin in the blood. In some such cases artificial immunity can be produced by the injection of dead or disintegrated bacilli. In preparing such immunizing agents, the bacteria may be killed by heat or chemical agents, they may be dissolved, or they may be destroyed mechanically by being ground into a very fine powder. The immunity conferred by the injection of such preparations can hardly be expected to be as efficacious as that which results from the natural disease or the use of living virulent organisms; first, because the process of killing the bacteria may destroy certain substances which give rise to immunity, and, second, because the injection of one or more doses of vaccine is hardly comparable with the continuous stimulus to which the body is subjected when microörganisms are permitted to multiply within its tissues. Nevertheless, satisfactory protection has been produced by this means against plague, cholera, and typhoid fever. Vaccination against typhoid fever with cultures killed by heat has been made compulsory in the United States Army, and it has resulted in an almost complete disappearance of this disease among the troops, even when they have been mobilized in districts where typhoid fever prevailed. The statistics for our army, as compiled by Russell, are shown in the following table:

TYPHOID FEVER, 1907 TO 1913, FOR THE WHOLE UNITED STATES ARMY. COMPULSATORY VACCINATION FOR THOSE UNDER 45 YEARS INTRODUCED IN 1911

Year	Mean Strength	Cases		Deaths		Occurring among those Vaccinated	
		No.	%	No.	%	Cases	Deaths
1907	62,523	237	3.79	19	0.30	..	..
1908	74,692	239	3.20	24	0.31	..	..
1909	84,077	282	3.35	22	0.26	1	0
1910	81,474	198	2.43	14	0.17	7	0
1911	82,802	70	0.85	8	0.10	11	0
1912	88,478	27	0.31	4	0.04	8	0
1913	90,646	3	0.03	0	0.00	1	0

(b) *Passive Immunity*

The immunity that follows an infectious disease, naturally acquired or produced by inoculation, as well as the immunity that results from the introduction of dead bacteria or bacterial products into the body, depends upon a reaction on the part of the tissues of the host. It is an active immunity. Such an immunity develops slowly, but when once established it is more or less durable. Numerous attempts have been made to transfer this immunity to non-infected animals by injecting into them the blood or blood serum of actively immune animals. When immunity results from such an injection it is spoken of as a passive immunity. In contradistinction to active immunity this type develops almost immediately after the injection, but it is never very durable.

Antitoxic Type.—Passive immunization has been most successful in those cases where the active immunity was due to the presence of antitoxins in the blood. It has been widely used in the treatment of diphtheria and in the prophylaxis and treatment of tetanus, and it is effective against the vegetable poisons, ricin and abrin, and against various snake venoms.

Other Forms.—Numerous attempts have been made to establish a passive immunity against those infectious agents which produce no soluble toxins. The transferal of such an immunity from the immune to the healthy animal has not been so successful as the transferal of antitoxins. The conditions here are extremely complicated, and the consideration of such measures must be deferred until the nature of this type of immunity has been more fully discussed.

Infant Immunity.—A special form of passive immunity is that which is conferred by the mother upon her infant. Ehrlich studied the transmission of immunity against the vegetable poisons, ricin and abrin. He showed, in the first place, that resistance to these poisons could be trans-

mitted to the new-born offspring from an immune mother but not from an immune father. In the second place, if the young of an immune female were nursed by a non-immune, they lost their immunity in about three weeks; whereas if the young of a non-immune were nursed by an immune animal they acquired an immunity. Evidently, therefore, the immunity to ricin can be transferred both to the fetus in utero, and to the nursing offspring by the milk. Like other forms of passive immunity, however, it is not very durable. These experiments have since been repeated upon a variety of animals and with a variety of infections. In certain cases, Ehrlich's results have been confirmed; in other cases the immunity has not been transmitted. The relations are evidently quite complicated and all immune bodies are not transmitted with equal ease.

It is well known that certain of the infectious diseases of childhood occur with relative infrequency during the first year of life. Among these are scarlet fever, measles, rubeola and diphtheria; and it is not improbable that in these cases the relative immunity of very young infants is due to protective substances derived from the mother. In the case of diphtheria, as we have seen, the antitoxic content of the blood, as estimated by the Schick reaction, is as a rule greater under one year of age than in later infancy and childhood.

Mechanism of Antitoxic Immunity

Toxin and Antitoxin

We have seen that toxins are soluble poisonous products of bacterial growth. Aside from their physiological action, little is known about them. Chemically, they are closely related to the proteins and even the purest preparations of bacterial toxins thus far obtained give some protein reactions. Toxins are sensitive to heat and are usually destroyed when in solution by temperatures of 80° C. or less. Biologically, the toxins are characterized by the fact that when proper doses are injected into certain animals the blood sera of the latter acquire the property of counteracting the effect of the particular toxin used. Such sera contain antitoxin. Among pathogenic bacteria the most important toxin producers are the diphtheria bacillus, the tetanus bacillus, the Bacillus botulinus, the Bacillus pyocyaneus and the Bacillus of symptomatic anthrax. It has also been claimed that soluble toxins are produced by typhoid, cholera and dysentery bacilli; but even admitting that this be true, it is, nevertheless, certain that the symptoms of these diseases are not due in any large measure to these substances. Similar to the toxins are those soluble poisons, secreted by certain bacteria, which possess the property of hemolyzing red corpuscles. Furthermore, the staphylococcus aureus secretes a

poison which directly and visibly injures the white corpuscles of the host (leukocydin).

Other Substances that Behave Like Toxins.—Substances having many chemical, physical and biological reactions of the toxins may be derived from sources other than bacteria. Thus ricin from the castor oil bean, abrin from the jequirity bean, and crotin from the Croton tiglium, as well as other plant derivatives have such properties. Snake venoms and spider poison are similar substances derived from animal sources. All of these produce specific antitoxins when injected into animals. Snake venoms, however, differ from bacterial toxins in that they are more resistant to the action of heat.

FERMENTS.—Ferments in general, though less poisonous than toxins, nevertheless possess many points with them in common. They are sensitive to heat, they cannot be separated easily from proteins, and when injected into the animal body they give rise to antiferments. Many, therefore, have classed toxins with the ferments.

Neutralization of Toxin by Antitoxin

The older view, that an antitoxin renders the corresponding toxin inert by decomposing it, has now been generally abandoned. Inert mixtures of the two have been made poisonous by measures which destroyed the antitoxin in the mixture. Thus Morgenroth found that when a small amount of hydrochloric acid was added to a neutral mixture of snake venom and its antitoxin, the latter could be destroyed by heating, and the toxin was left in a free and active state. Such experiments indicate that antitoxin neutralizes the toxin in somewhat the same manner that an acid neutralizes a base. The toxin is rendered inert because it enters into combination with the antitoxin.

Effect of Adding Toxin to Neutral Toxin-antitoxin Mixtures.—Quantitative studies of the neutralization of diphtheria toxin by antitoxin have shown, however, that the reaction is by no means so simple as that which takes place between strong acids and bases. When an exactly neutral toxin-antitoxin mixture is prepared, it is found that considerably more than a fatal dose of toxin must be added in order that the mixture cause the death of a guinea-pig. Let us assume, for example, that 0.01 c.c. is the minimum amount of a certain solution of diphtheria toxin that will kill a guinea-pig in three to four days. Let us assume, furthermore, that it requires 1.00 c.c. of this toxin solution to make a neutral mixture with one standard antitoxin unit. If further toxin be added, the mixture will cause some manifestation of disease, such as a local reaction at the point of injection or a late paralysis. In order to cause the death of a guinea-pig in three or four days, however, it may be necessary to add to the neutral mixture 1.00 c.c. of the toxin solution.

In other words, 100 times the minimum fatal dose may have to be added in order to make the neutral mixture fatal within the specified time. This discrepancy between the minimum fatal dose of pure toxin and the amount of toxin which must be added to a neutral mixture of toxin and antitoxin in order to be fatal has received various explanations.

Ehrlich's Explanatory Hypothesis.—According to Ehrlich, solutions of diphtheria toxin contain two types of substances. The first of these, or toxin proper, possesses both a high toxicity and the property of uniting with antitoxin. The second group (toxon and toxoid) combine with antitoxin but their toxicity is relatively slight. When the solution of diphtheria toxin is completely neutralized by antitoxin, both toxin and toxon are neutralized. If more diphtheria toxin solution be added to the mixture, the true toxin contained therein will displace the toxon from its antitoxin combination and the free toxon may then produce such symptoms as a local reaction or a late paralysis. It fails, however, to produce death in the specified time of three or four days. Only when the antitoxin is completely saturated with toxin is an excess of the latter able to cause the death of the animal in the specified time.

Ehrlich showed, furthermore, that while the toxicity of a solution of diphtheria toxin diminishes rapidly, shortly after it has been prepared, there is no marked change in the amount required to neutralize a standard antitoxin unit. He believes that toxins have become converted into toxoids.

Opposing Hypotheses.—According to Ehrlich's hypothesis, therefore, diphtheria toxin is a complex mixture of bacterial substances which are capable of neutralizing antitoxin but which possess different degrees of toxicity. The "haptophore" group of atoms by which these substances combine with antitoxin is identical. The "toxophore" groups to which they owe their toxic action differ. Ehrlich's view that toxin solutions contain a number of substances with varying degrees of toxicity is disputed by Arrhenius and Madsen, who hold that the observations concerning the toxicity of toxin-antitoxin mixtures may be explained, if we assume that these substances do not behave like mixtures of strong acids and bases, but rather like mixtures of weak acids and bases. In such mixtures a portion of each substance remains free in the solution. Bordet believes that when antitoxin is added to a toxin solution in amounts insufficient to effect a complete neutralization, it does not leave a certain portion of the toxin free in solution, but distributes itself over all the molecules of the toxin and partially neutralizes each one of these so that their toxicity is modified but not destroyed. Bordet compares the reaction between toxin and antitoxin to the staining of starch paste with iodin, where varying amounts of the latter are absorbed by the former with the production of colors of varying intensity. This "absorption" theory of the reaction between toxin and antitoxin explains the observed facts in a

fairly satisfactory manner, and is in accordance with the laws governing reactions between colloidal substances.

The Formation of Antitoxins

The early view of Buchner and others, that antitoxins are formed by some chemical transformation of the toxins in the body, is now definitely disproven. The amount of antitoxin formed may be altogether too great to be accounted for in this manner. Thus Knorr has shown that 100,000 units of antitoxin may be produced in response to a dose of toxin that corresponds to a single antitoxic unit, and others have shown that the antitoxin production in the blood continues even after the entire amount of blood has been removed by repeated bleeding. It is now universally held that the formation of antitoxin represents a specific response on the part of the body cells to a specific poisoning or irritation by the toxin.

Side-chain Theory.—The nature of this response has been formulated by Ehrlich in his now famous side-chain theory. Not only toxins but a variety of other substances give rise to antibodies of one form or another when they are introduced into the animal body. Such substances which possess the property of giving rise to antibodies are spoken of in general as antigens. Ehrlich conceives that when such antigens are introduced into the body they enter into combination with certain of the body cells because they possess atomic complexes (haptophore groups) that unite with atomic complexes (side-chains) of the body cells. Through this combination the antigen is able to act upon the cells of the body, and the latter may be damaged or irritated. The side-chains with which the toxin has united are rendered useless and the cells proceed to form new side-chains of a similar character. This formation, however, is usually excessive, for it is a general biological law that irritation or damage leads to an overproduction of the damaged tissues. The new side-chains thus produced in excessive numbers are cast off into the circulation as free molecules. If new toxin be now introduced into the blood it combines with and is neutralized by these free side-chains in the body fluids. In this manner it is prevented from attacking and injuring the body cells. According to Ehrlich's hypothesis, therefore, antitoxin is nothing more than the sum of the free side-chains which have been produced by, and given off from, the body cells in response to a specific injury by toxin (Fig. 111).

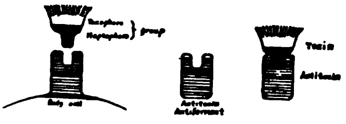

Fig. 111.—The Relation of Toxin to Antitoxin, According to Ehrlich.

Affinity Between Toxin and Susceptible Tissue.—The side-chain theory postulates that the toxin enters into a chemical combination with the cells that it injures and that these cells in turn produce the specific protective antitoxin. Many experiments have been made in order to demon-

strate that susceptible tissues have a peculiar affinity for the toxin that injures them. It has been shown, for example, that various toxins when injected into susceptible animals disappear rapidly from the circulating blood; whereas when they are injected into certain non-susceptible animals, no such prompt disappearance takes place. Pigeons, for example, are only slightly susceptible to tetanus and the tetanus toxin may be demonstrated in the blood, liver, spleen, kidneys and muscles for several days after an injection. None is found in the central nervous system, however, apparently because that which is taken up here is either neutralized or destroyed. Lizards are practically insusceptible to tetanus, and when tetanus toxin is injected into these animals it may be demonstrated in the blood as long as two months after the injection. It has been shown, furthermore, that a pulp made from the nervous tissue of susceptible animals will neutralize the tetanus toxin in much the same way as antitoxin does, apparently because it contains substances which combine with the toxin. The nervous tissue of relatively insusceptible animals, such as chickens, has a weaker neutralizing power, and the nervous tissue of very insusceptible animals, such as the frog and turtle, is almost without neutralizing action. There seems, therefore, to be a definite relation between the affinity of the nerve cells for tetanus toxin and the natural susceptibility of the animal. Other toxins which act upon the nervous system also combine with these tissues.

Reaction in Nerve Tissue With Lipoids or Proteins.—It has been suggested that the peculiar affinity between tetanus toxin and nervous tissue may depend, not upon a chemical combination between the toxin and the nerve proteins, but upon some physical or chemical reaction with the lipoids that are so abundant in nerve tissues. That lipoids possess a peculiar relationship to toxins is certain. It seems improbable, however, that this can account for the differences observed between susceptible and non-susceptible animals. Furthermore, the binding character of the nervous tissues may be destroyed by heat—a fact which favors the view that the affinity depends in large measure upon protein substances present in the cells.

Time Needed for Reaction.—Time is required to complete the reaction between toxin and antitoxin or between toxin and body cells. When a mixture of toxin and antitoxin is allowed to stand for half an hour it may be completely innocuous, whereas the same mixture if injected immediately may cause symptoms, for the reason that some of the toxin has escaped neutralization. Similar relations seem to hold with respect to the union of toxin to the cells of the body. When toxin is injected into an animal and antitoxin is subsequently administered, the protective influence of the latter diminishes rapidly as time elapses between the two injections. After a few hours, the union between the body cells and the toxin may be so firm that no dose of antitoxin, however

large, is able to save the animal. This fact is of great practical importance, since it indicates the necessity for early therapeutic injections of antitoxin. In the case of tetanus, for example, prophylactic injections of antitoxin are of undoubted value, whereas the injection of antitoxin after symptoms have developed often fails to modify the clinical picture. The therapeutic value of antitoxin lies mainly in the fact that it neutralizes any fresh toxin that may be produced in the body. Possibly also it breaks up recently formed and still unstable unions between the tissues and the toxin.

Susceptibility of Frogs to Tetanus Toxin.—It has been pointed out that tetanus toxin is not readily taken up by the nerve tissues of animals that are insusceptible to the disease. In the case of frogs the toxin may be demonstrated in the circulation for months after an injection. It has been shown that if such frogs be warmed to 25° to 30° the animals may develop the disease. This is due in part to the fact that at these temperatures the toxin combines more readily with the nervous tissues. As Morgenroth has shown, however, some tetanus toxin may be bound by the nerve cells of these animals even at low temperatures and this may produce toxic symptoms only when the animals are heated. Apparently some union with the body cells takes place at low temperatures, whereas a higher temperature is required in order that the toxin produce its poisoncus effects.

Union of Toxin and Cell Prerequisites of Antitoxin.—That a union between toxin and cell is a necessary prerequisite for the formation of antitoxin is supported by the fact that the frog and turtle form no antitoxin. It should be remembered, however, that the mere failure to produce symptoms does not necessarily indicate that no union between toxin and body cells has taken place. The alligator and the hen, for example, though highly resistant to tetanus, nevertheless form antitoxin in considerable amounts, apparently because the toxin unites with other tissues than the central nervous system, and these other tissues furnish the antitoxin without, however, giving rise to the characteristic nervous manifestations of the disease. The formation of antibodies may be a purely local phenomenon. Thus Römer produced an immunity to abrin by dropping it into one eye of a rabbit and then showed that the conjunctiva of this eye contained abundant antitoxin, whereas the conjunctiva of the opposite eye contained little or none.

Bactericidal Properties of Blood Serum

When an infecting microörganism produces symptoms mainly through a soluble toxin, the subsequent immunity is due largely to the formation of a specific antitoxin. In most infectious diseases, however, no soluble toxin is formed and the subsequent immunity is due to some mechanism

which acts against the bacteria themselves. It is an antibacterial immunity. Such an immunity may depend either upon changes in the body fluids (humoral immunity) or upon changes in the activities of the body cells and particularly of the leukocytes that come into the neighborhood of the infecting bacteria (cellular immunity).

Alexins.—The natural bactericidal properties of blood were indicated by John Hunter's observations that blood does not decompose so readily as do other putrescible materials. Many years passed, however, before it became possible for Nuttall and others to show that when bacteria are added to fresh blood or blood serum a considerable number could be destroyed, and that heating the blood to 60° C. caused it to lose this property. The substances which killed the bacteria were spoken of as alexins.

Bacteriolysis.—In certain forms of immunity the bactericidal properties of the blood are increased. Pfeiffer found that when cholera spirilla were injected into the peritoneal cavity of an immunized guinea-pig they rapidly disintegrated (bacteriolysis); whereas the same amount injected into the peritoneal cavity of a non-immune animal multiplied and caused death. If other bacteria were used, no difference could be observed between the normal and the cholera-immune animals. The reaction was, therefore, a specific one. Pfeiffer showed, furthermore, that if serum from an immunized animal were mixed with the spirilla and the mixture were injected into the peritoneal cavity of a normal guinea-pig, the spirilla were rapidly destroyed just as in an immune animal, and that this occurred even though the immune serum had previously been heated so as to destroy completely its bactericidal properties.

Two Substances of Immune Serum.—Bacteriolysis has also been observed and studied outside of the animal body. Fresh normal serum has little effect upon the cholera spirilla. Serum from an immune animal has a powerful bacteriolytic action but loses this when heated to 60° C. If, however, the heated immune serum be mixed with fresh normal serum it regains its bacteriolytic properties. Evidently two substances are present in such bacteriolytic serum. One is heat resistant and is contained in the immune serum. The other is readily destroyed by heat and is present in normal as well as in immune serum.

Other Reactions of Same Type; Hemolysis.—Further studies have shown that the development of bacteriolytic properties in response to bacterial injections is but one of a general group of reactions of this type. Various foreign cells when injected into an animal may give rise to the production of specific cytolytic substances. The reactions following the injection of alien red blood corpuscles have been particularly studied. If the erythrocytes of an animal *A* be injected into an animal *B*, the blood serum of *B* frequently acquires the property of hemolyzing the erythrocytes of *A*. This hemolysis, like the bacteriolysis produced by immune serum, is due to the action of two substances. The first, which

is resistant to moderate heat, is greatly increased during the process of immunization and it is specific for the corpuscles injected. It is spoken of as the immune body, the amboceptor or the sensitizer. The second, which is readily destroyed by heat, is not increased during immunization. It is called the complement.

Amboceptor and Complement

When a specific hemolytic serum prepared by injecting foreign red corpuscles into an animal is heated to 55° C. for an hour, the complement is destroyed and the hemolyzing properties disappear. The serum is said to have become inactivated. Inactivation does not, however, destroy the amboceptor, for the hemolytic properties are restored by the addition of fresh non-immune serum which contains complement but in itself may cause no hemolysis.

Affinity of Red Cells for Specific Amboceptor.—The red corpuscles possess a strong affinity for their specific amboceptors. When mixed with an inactivated immune serum and later separated by centrifugalization they carry the amboceptor out with them. The serum loses some or all of its amboceptor and the red cells are now readily hemolyzed by the complement of normal sera. When red cells are mixed with a hemolytic serum at a temperature of 0° C. no hemolysis occurs. If the cells are then separated from the serum without raising its temperature they carry the amboceptor out with them, but leave the complement behind. At this low temperature a union occurs between the cells and the amboceptor, but the complement does not fix itself to the cells and no hemolysis occurs.

Formation and Action of Amboceptor.—We have seen that immunization against foreign cells causes a marked increase in the amount of amboceptor in the blood. Ehrlich conceives that material from the injected cells, like antigens in general, is bound by certain "side-chains" on the body cells and that the subsequent multiplication and liberation of these side-chains give rise to the amboceptors which have a special affinity for the injected cells. Unlike antitoxins, however, these immune bodies require the presence of a second substance, the complement, in order to manifest their activity. Ehrlich believes that the complement is unable to unite with the foreign cells directly and that it does this only through the medium of the amboceptors. Schematically his views are expressed in Figure 112.

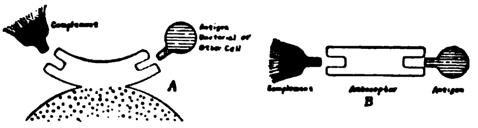

Fig. 112.—The Relation of Amboceptor to Antigen and to Complement, According to Ehrlich.

Bordet's Opposing Hypothesis.—Bordet, on the other hand, believes that no definite proof has been offered for the view that the ambo-

ceptor acts as an intermediary body between cell and complement. He believes that the immune body, which he calls the sensitizer, unites with the cells and changes them in some way so that they become sensitive to the direct action of the complement. The exact nature of the change is not known, but the point is emphasized that the complement unites not with the amboceptor alone but with the cell itself, after the latter has been properly prepared by absorption of amboceptor. Ehrlich and his school have sought to support their view by proving that union between the amboceptor and complement may occur without the participation of the antigenic cells, but the evidence thus far submitted has not received general acceptance.

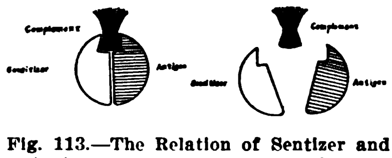

Fig. 113.—The Relation of Sentizer and Antigen to Complement, as Given by Zinsser, to Represent the View of Bordet. (Redrawn from Zinsser, "Infection and Resistance.")

Chemical Properties of Amboceptor.—Concerning the nature of the amboceptor relatively little is known. We have seen that it is resistant to moderate heat. It may be preserved for long periods of time, particularly when kept in the dark and at a low temperature. Its colloidal character is indicated by the fact that it does not pass through an animal membrane. It is precipitated with the globulins of the blood serum but its protein nature is not established.

Site of Formation.—The specific immune bodies against the cholera spirilla are formed particularly in the spleen, the bone marrow, and the lymphatic glands, yet the removal of the spleen does not materially affect this formation in the body. Amboceptor may also be formed locally and has been demonstrated to be most abundant in the region where the foreign cells have been injected.

Characteristics of Complement.—The complement is very sensitive to heat and is quickly destroyed by temperatures of 50° to 60° C. When serum is preserved the amount of the complement diminishes rapidly. Immunization does not increase the amount of complement in the body. Furthermore, the complement has not the highly specific character of the amboceptor, and apparently the same complement may enter into a variety of reactions provided the proper antigen and amboceptor are present.

Isohemolysins—Autohemolysins

We have seen that it is possible to induce the formation of specific hemolysins by the injection of red corpuscles from animals of one species into animals of a different species. The injection of red corpuscles from one animal into other animals of the same species may or may not lead to the production of hemolytic substances against the injected corpuscles. When such hemolysins are formed they are spoken of as isohemolysins.

Isohemolysins may also occur naturally, and they account for some of the occasional accidents which have followed the direct transfusion of blood from one individual into another of the same species (page 606). When an animal is injected with his own red corpuscles no hemolysins against these are formed, nor do autohemolysins normally result from the disintegration of blood within the body. It is evident, therefore, that the immune reactions of which hemolysis may be taken as an example, are reactions against foreign cells and that they do not ordinarily occur when cells disintegrate within the body.

Specificity of Cytolysins

Thus far we have spoken of the immune bodies that are produced in response to the injection of foreign cells as being specific for the cells injected. While this is true in a general way the statement requires certain modifications. Cytolysins affect not only the cells used for their production but also closely related cells, and by determining the extent to which this occurs one may estimate the biological relationship between different types of cells. It has been found, for example, that when an isohemolytic serum has been prepared by injecting the red corpuscles of one animal into another of the same species, this serum not only destroys the red corpuscles of the animal which has furnished them but also destroys the red corpuscles of certain other animals of the same species. On the other hand, it is inactive against corpuscles of the treated animal as well as against the red corpuscles of certain other animals of the same species. On the basis of such a test, therefore, one may establish biological relationships or differences between groups of animals belonging to a single species. As we shall see, the same principle applies in other immune reactions.

Cytotoxins Specific for the Animal Rather Than the Organ.—Different tissues from a single individual may show similar biological reactions. Specific antibodies have been prepared not only against the red corpuscles but against spermatozoa, ciliated epithelium, and other cells. It has been suggested that by this means it might be possible to prepare specific toxic substances which would act only on certain tissues, and that by the use of such specific cytotoxins one might be able to induce pathological changes or toxic manifestations in any particular organ. Experience has shown, however, that with but few exceptions this is not the case. Cytotoxins prepared by the injection of washed and macerated tissues have, in general, been toxic not for these organs alone but for other tissues of the same animal, and particularly for the red corpuscles. From the biological standpoint, therefore, the relationship between the various cells of a single individual is, as a rule, more intimate than is the biological relationship between the corresponding cells (e. g., the red corpuscles) of different species of animals.

Immunity and the Bactericidal Properties of Blood Serum

The increased bactericidal properties of the serum in animals immunized against cholera, typhoid, and certain other infections, raised the hope that herein might be found an explanation for all those forms of immunity that depend upon the antibacterial activities of the infected animal. It soon appeared, however, that this generalization was not correct. In many infections and particularly in those produced by the pneumococcus, the streptococcus and the anthrax bacillus, the bactericidal properties of the blood serum do not run parallel to the degree of immunity.

Further Objections to Bactericidal Theory.—Furthermore, animals that have been immunized against cholera or typhoid and that yield strongly bactericidal sera and are quite resistant to intraperitoneal injections of these bacilli, may yet be relatively susceptible to infection if the same bacteria are introduced subcutaneously or by way of the alimentary tract. Possibly the local character of these infections may interfere with the protective activities of the body fluids or possibly the doses given were relatively large when compared with the small numbers that probably suffice to produce the natural diseases in man.

Those who have opposed the bactericidal doctrine of immunity furthermore emphasize the fact that bacteria may persist in the bodies of so-called bacillus carriers for years, even though the blood serum possesses marked bactericidal properties. This persistence undoubtedly depends in part upon the local conditions about the infection which interfere with the free access of the body fluids. In addition, it depends upon the fact that under these circumstances a strain of bacteria is developed that is resistant to the antibacterial activities of the blood serum. The bacteria have become "serum fast."

Those who support the bactericidal doctrine of immunity now admit its limitations, first as regards certain infections, such as those with anthrax bacilli and the cocci, and second as regards certain local infections and infections with "serum fast" organisms. Nevertheless, they maintain that in certain infectious diseases, such as typhoid and cholera, an increased bactericidal activity of the body fluids plays an important part in warding off subsequent infection with the relatively small numbers of organisms that ordinarily enter the body at any one time.

Antibacterial Substances Present in Plasma.—From the first, Metchnikoff and his school have opposed the entire humoral doctrine of immunity, and have emphasized the importance of the phagocytic activity of certain cells in protecting the body against the infectious diseases. They have maintained that the antibacterial properties of blood serum do not exist in the unshed blood plasma, and that the serum owes its bactericidal properties to substances derived from the leukocytes during

the process of clotting. The question is a difficult one to decide, for it is practically impossible to prove that the bactericidal properties of blood may not have changed after its withdrawal from the blood vessels. However, the majority of those who have worked with cell-free blood plasma that has been kept from coagulating by various means have found that such plasma possesses the same bactericidal properties as blood serum. It seems highly probable, therefore, that these antibacterial substances are present as such in the body fluids and that they are not formed after the blood has been drawn.

Antibacterial Immunity Complex and Varied.—The controversy between those who supported the humoral theory of immunity, and those who attributed immunity to the phagocytic action of certain cells in the body, has shown that the immunity which depends upon the antibacterial activities of the body is of a complex nature and is not the same in all cases. In certain diseases, the body owes at least a part of its immunity solely to changes in the body fluids. In other diseases, more dependence is placed upon the direct activity of the body cells. Even here, however, as we shall see, the activity of the cells is greatly influenced by substances present in the body fluids (see Opsonins). Thus the discussion as to which doctrine is correct has given way to attempts to determine the relative parts played by cells and fluids in various types of infection.

Complement Fixation

In studying the mechanism of immunity a number of methods have been discovered which have proved of great value in the diagnosis of infections. Among these is the method of complement fixation. Bordet and Gengou showed that when heated immune serum was mixed with the specific bacteria used in its production the mixture was capable of fixing the complement in a fresh non-immune serum. If red corpuscles and their specific immune bodies were subsequently added to this mixture no hemolysis occurred, because all of the complement had been fixed by the bacteria and their immune bodies. These relationships are represented graphically in terms of the Ehrlich hypothesis in the accompanying diagram.

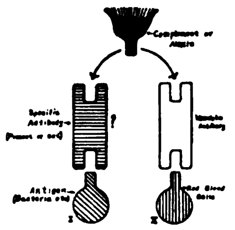

Fig. 114.—Schematic Representation of the Complement Fixation Reaction. If the Blood Contains a Specific Antibody for a Given Antigen, It Will Fix the Complement and the Subsequent Addition of Red Cells and Their Specific Antibodies Cause No Hemolysis. If Hemolysis Occurs It Indicates an Absence of the Specific Antibody for a Given Antigen. (Redrawn from Zinsser, "Infection and Resistance.")

Later Gengou showed that the complement fixation reaction was not limited to mixtures of cells and their specific antibodies, but that it also occurred when various dissolved proteins, such as egg white, dog's serum, etc., were brought in con-

tact with the sera of animals which had previously received injections of these same proteins.

Method of Using Test.—The great value of complement fixation, both as a practical diagnostic measure and as a means of approaching certain theoretical problems, has now been conclusively proven. The blood serum of patients suspected of suffering from a given infection is first heated and is then mixed with the microörganisms in question, or, better still, with extracts derived from these organisms. To this mixture fresh serum containing complement is added. After allowing the mixture to stand for a time, red corpuscles from another animal together with an inactivated immune hemolytic serum (amboceptor) against these corpuscles are added. If the complement in the fresh serum has been fixed by the original mixture, no hemolysis occurs. The antibodies in the patient's serum have united with the antigen added and this combination has fixed the complement present. The suspected serum from the patient contains antibodies against the disease in question. If, on the other hand, hemolysis occurs, the complement was not fixed and no antibodies against the disease in question were present in the patient's serum.

Applications of Complement Fixation.—The complement fixation test has been used with success in the diagnosis of chronic gonorrheal infections, glanders, echinococcus and other infections. It has proved a very delicate test for recognizing the origin of certain proteins and particularly for determining the source of very small amounts of blood, being more sensitive than the precipitin test that will be described later.

Wassermann Reaction for Syphilis.—The complement fixation test has found its widest practical application in the diagnosis of syphilis. Wassermann's discovery of this reaction was based upon the reasoning already given. Organs rich in spirochetes were extracted. This extract when mixed with the blood serum of syphilitic patients was found to fix complement and to prevent hemolysis when red cells and their specific immune amboceptors were subsequently added to the mixture. Later work has shown, however, that it is not necessary to use organs containing the spirochetes of syphilis in performing the Wassermann reaction. Extracts prepared from the heart muscle as well as other organs of normal animals will also fix complement when mixed with the blood serum of syphilitics. Even a one per cent solution of commercial lecithin has been used for this purpose. Furthermore, extracts prepared from pure cultures of syphilitic spirochetes do not regularly fix complement when mixed with syphilitic blood and they cannot be used in practical diagnostic work. It is evident, therefore, that the Wassermann reaction does not depend upon a fixation of complement by a union of substances derived from the spirochetes with antibodies present in the patient's blood. From the theoretical standpoint it is not a specific test for the spirocheta pallida. The nature of the reaction is by no means clear. Most antigens which have been used

successfully in Wassermann tests are of a lipoidal character, and it would seem that these combine with some substance present in the serum of syphilitic patients, and that this combination is capable of fixing complement.

Despite the fact that the Wassermann reaction has been shown to depend upon other substances than the syphilitic spirochetes, its great value in the diagnosis of syphilis has been amply proven by innumerable clinical tests. The reaction is practically never obtained with blood serum of normal individuals. Experience has shown, indeed, that it may be positive in certain other diseases than syphilis, among which are yaws, trypanosomiasis, scarlet fever, etc. Its diagnostic value is not greatly lessened by this fact, for these diseases are either rare in temperate climates or they can be readily differentiated from syphilis by other means.

Agglutination

In studying the effect of immune sera upon the bacteria used in immunization, it was early noted that when minute quantities of such sera were added to a liquid suspension of the homologous bacteria the latter often formed clumps. This phenomenon is called agglutination. If a hanging drop preparation is studied under the microscope, it is seen that motile bacteria soon lose their motility and then gradually gather together into groups, leaving the intervening fluid free of microörganisms. If the bacterial suspension and the immune serum are mixed in small test tubes the process becomes evident by the disappearance of the uniform cloudiness and the formation of a sediment composed of the clumped bacilli.

Method for Identifying Bacteria.—The phenomenon of agglutination is relatively specific for the microörganisms used, and it has found a variety of applications. On the one hand, the serum of an animal immunized against a particular strain of bacteria may be used for the purpose of identifying unknown bacteria. For example, Cole and his associates have recently used this method for the rapid recognition of the various types of pneumococcus present in patients suffering from pneumonia.

Agglutination Tests in Infections.—On the other hand, the serum of a patient suffering from an acute infection may be tested to determine whether or not it contains agglutinins with respect to known bacteria. This test has proved of particular value in the recognition of typhoid fever, paratyphoid fever, Malta fever, and dysentery. Experimentally, a large number of agglutinins have been produced. The practical diagnostic value of the reaction is restricted, however, by the fact that agglutinins usually do not develop until rather late in the disease. Where an infection, such as typhoid fever, is prolonged, the development of agglu-

tinative properties after seven to ten days of the disease may still be of great diagnostic value. In more acute infections, such as plague, however, an equally late development of agglutinins robs the test of much of its practical value.

Agglutination occurs with non-motile as well as with motile organisms. It may also be obtained with dead organisms, a fact which has been utilized in the Ficker method of diagnosing typhoid fever.

Quantitative Tests Necessary.—Agglutination tests are specific only in a quantitative sense. In low dilutions the sera of certain normal individuals agglutinate the typhoid bacilli. In order to eliminate this source of error in diagnostic work it is necessary to dilute the serum tested, dilutions of one to forty being commonly used. The origin of the agglutinins in normal sera is not known, but the interesting fact that they are not present in the new-born suggests the possibility that they may have arisen from very mild unrecognized infections with typhoid or with related organisms, or that they may be due to the absorption of bacterial products from the intestines. The necessity for quantitative agglutination tests has also become apparent from the study of the sera of highly immunized animals. It has been found that such sera not only agglutinate the organisms used during immunization, but that they may also agglutinate other strains of bacteria. For example, the sera of animals which have been immunized against typhoid agglutinate not only the Bacillus typhosis but also suspensions of paratyphoid bacilli and even colon or other bacteria. The latter, however, are never agglutinated in as high dilutions as is the typhoid bacillus. Furthermore, if any of these other organisms are added to the immune serum and later separated by centrifugalization they remove all or nearly all the agglutinins that act upon them, but leave behind the major part of the typhoid agglutinin. It is evident, therefore, that the agglutinins formed in response to immunization with typhoid bacilli are of various kinds. Some of these, the so-called group agglutinins, react with the certain other bacteria, while others are strictly specific for the typhoid bacillus alone. The specificity of an immune serum can, therefore, be demonstrated either by using high dilutions or by absorption experiments.

Failure to Agglutinate at Low Dilutions.—Quantitative tests have also shown that in certain cases the immune serum agglutinates better at high than at low dilutions. The cause of this anomaly is not well understood. It has been suggested that "proagglutinoids" may be present which unite with the bacteria but do not produce agglutination, and that these prevent the union with the true agglutinins. On the other hand, it is possible that here, as in other colloidal reactions, the substances must be mixed in definite proportions in order to produce the reaction.

Resistant Strains of Bacilli.—Quantitative studies have also shown that agglutination depends not only upon the agglutinative strength of

the serum used but also upon the bacteria. An excess of bacteria in the mixture may interfere with the reaction. More important, however, is the fact that certain strains of bacilli are relatively resistant to agglutination. It has been noted repeatedly that typhoid bacilli, freshly isolated from the blood of patients suffering from the disease, are relatively resistant to agglutination, and the same is true if bacteria are cultivated in an inactivated immune serum. This resistance to agglutination is usually associated with an increased resistance to bacteriolysis by the immune serum. It indicates that bacteria may develop a certain immunity to the attacks of the host. They become serum fast. The exact cause of this resistance to agglutination is not well understood, but it seems to depend upon some change in the bacteria whereby a union with the agglutinins is interfered with.

Agglutination of Other Cells.—The phenomenon of agglutination is not restricted to bacteria but also occurs when immune sera, prepared by the injection of other foreign cells into the body, are mixed with the cells used. Red corpuscles, for example, are agglutinated by a homolgous immune serum after the hemolyzing properties have been destroyed by heating. Indeed, the blood sera of certain normal individuals agglutinate the red corpuscles of certain other individuals of the same species, and human bloods have been divided into several classes, the classification being based on the presence of such "iso-agglutinins." The practical significance of such substances in the transfusion of human blood is discussed elsewhere (page 606).

Agglutinins in Ehrlich Theory.—According to Ehrlich's theory, agglutinins, like other antibodies, are molecular complexes or side-chains, which combine with the proteins of foreign cells and which are given off from the body cells in consequence of a previous union of the foreign proteins with the body cells (page 515). Ehrlich conceives that the agglutinins consist of two portions. The one unites with the foreign protein, while the other causes agglutination. His views are expressed in Figure 115.

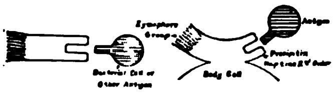

Fig. 115.—Schematic Representation of the Formation and Reaction of Precipitins, According to Ehrlich.

Nature of Agglutinin Reaction Obscure.—The nature of the reaction between the agglutinins and the cells which they agglutinate is not well understood. The reaction does not depend upon the motility or flagellated character of the reacting organisms, for non-motile, non-flagellated bacteria may be agglutinated by their homologous sera. The reaction has many features in common with the precipitation of proteins by their specific precipitins and it seems probable indeed that the two reactions are identical in character. The nature of precipitins will be discussed at the end of the next section.

The Precipitin Reaction

In studying the formation of agglutinins it was noted by R. Kraus that when the sera of animals which have been treated with bacterial proteins were mixed in proper proportions with clear solutions of these proteins a precipitate was formed in the mixture. This reaction is a general one and can be obtained after almost any soluble protein has been injected into an animal. Precipitins like agglutinins withstand temperatures of 56° C. but are injured or destroyed at higher temperatures (70° C. or over). In neither case does the serum complement take part in the reaction.

Used for Identification of Proteins.—The reaction between a protein and its precipitin evidently belongs to the general group of immune reactions. It has found its main application, however, in the identification of various proteins and particularly in the recognition of the source of blood stains; a question that is often of great importance in forensic medicine. Like agglutination the precipitin reaction is relatively specific for the protein used. By immunizing an animal against human blood serum, for example, it is possible to produce precipitins of such potency that when mixed with human serum, diluted even to one hundred thousand times, a precipitate is still formed. In practice the blood serum is usually diluted one thousand times. When antihuman serum is mixed with the blood serum of another animal no precipitate ordinarily results. Only the sera of the higher monkeys and particularly of the chimpanzee, the gorilla and the ourang, give results at all comparable to those obtained with human sera, though even here not in such high dilutions. Blood sera from other monkeys may give precipitates with antihuman serum at low dilutions, or again they may fail to react at all. It is evident, therefore, that precipitin tests may shed light upon the biological relationship of animals—a fact which has been successfully used in deciding certain disputed points in zoölogy.

Organ Specificity and Species Specificity.—The antisera produced by the injection of different fluids or organ extracts from a given species of animals react not only with the fluids or extracts used, but also with most other protein solutions prepared from this same species. They fail to react with most proteins from other animal species. Here then, as in the case of the cytolytic sera (page 521), it is evident that a closer biological relationship exists between different organs of the same animal species than between the same organs of different animal species. To this rule the crystalline lens is an exception, for it is possible to produce a lens precipitin which does not react with the blood serum of the animal used but which does react with the lens protein of animals of different species. Protein from the crystalline lens, therefore,

shows an "organ specificity" but not a "species specificity." Substances from the testis may also show an organ specificity.

Failure from Excess of Either Substance.—The precipitation reaction may fail when either of the two reacting substances is present in excess. This is shown in the following table taken from Zinsser's "Infection and Resistance" (page 253):

Anti-sheep Serum from Rabbit	Sheep Serum 0.5 c.c. of Following Dilutions	Precipitation
0.5 c.c.	1:10	+ -
0.5 c.c.	1:100	+++
0.5 c.c.	1:500	+++
0.5 c.c.	1:1000	++
0.5 c.c.	1:5000	+
0.5 c.c.	1:10000	0

Explanatory Theories.—We have already noted that a somewhat similar relationship exists with respect to agglutination and that in some instances agglutination takes place more readily at fairly high than at very low dilutions of the serum. Ehrlich conceives that precipitins like agglutinins contain two distinct atomic complexes. One of these combines with the protein against which the antibodies are prepared, while the other causes the specific reaction. He explains the occasional failure of agglutination, when agglutinins are in excess, by assuming that there are present in the immune serum "proagglutinins" which unite with the bacteria without causing agglutination and which prevent the union of the true agglutinins. It is possible, however, as Zinsser and others have pointed out, that such failures may be due to the colloidal character of the reacting substances, for it is well known that colloidal reactions take place only when the reacting substances are present in the proper proportions. An excess of either may interfere with the precipitation or agglutination which would otherwise take place.

Phagocytosis

General Principles

When a cell possessing ameboid motion is placed in close relation to foreign particles or cells it not infrequently moves toward these foreign bodies, engulfs them in its interior and digests them. The motion of the cell toward a foreign particle is probably determined by chemical substances emanating from the latter and is spoken of as *chemotaxis.* The engulfing of foreign particles by the cell is spoken of as *phagocytosis.* The disappearance of the foreign body within the cell is due to *intracellular solution or digestion.*

Influences Determining Migration of Motile Cells.—These phenomena

are more or less independent of one another. They have been studied not only in the special case of ameboid cells derived from the bodies of higher animals, but also in unicellular organisms and in the lower plants and animals. The migration of motile cells and organisms is determined by a variety of influences, such as light, heat, gravity and the chemical constitution of the surrounding medium. The latter is of dominant importance in determining the ameboid movements of cells in the bodies of higher animals. Chemical substances may attract or repel motile cells and organisms, the effects varying with the chemical substances used, their concentration and character of the cells or organisms experimented upon. When ameboid cells are attracted, the phenomenon is called positive chemotaxis; when repelled, negative chemotaxis.

Phagocytosis Due in Part to Chemotaxis.—The engulfing of solid particles by motile ameboid cells, which is called phagocytosis, is in many cases at least an extension of the process of chemotaxis. The motile cell not only moves toward the region of the attracting chemical substances but having arrived there it surrounds the foreign body. In addition, it seems possible that mere contact with a solid particle may in some cases cause the phagocytic cell to enclose it. Chemically inert substances such as particles of coal dust or India-ink are often taken up by phagocytic cells.

Reaction Between Cell and Foreign Particle.—The subsequent fate of the foreign body within the phagocytic cell is determined by the mutual reaction between the cell and the foreign particle. Not infrequently the particle can be seen to undergo disintegration, apparently because it is digested by the intracellular ferments of the phagocytic cell. Proteolytic ferments have been prepared from the bodies of amebae, and the intracellular digestion in this case serves the useful purposes of nutrition. Polynuclear leukocytes also contain proteolytic ferments, which are active in an alkaline solution. On the other hand, the engulfed particles may exert a deleterious effect upon the cells which contain them; and bacteria, especially if taken in excessive numbers, may destroy the phagocytic cells.

Physical Explanation for Chemotaxis and Phagocytosis.—Attempts have been made to explain the phenomena of chemotaxis and phagocytosis in accordance with well-known physical and chemical laws. When small particles of one liquid are suspended in another liquid in which they are insoluble, the individual particles in suspension tend to assume spherical forms by virtue of the phenomenon of surface tension. If, for any reason, this surface tension is diminished on one side of the particle the latter loses its spherical shape and fluid is pushed out in the direction of the lessened surface tension. A "pseudopodium" is thus formed and the whole drop tends to move in the direction of the "pseudopodium." When it reaches a foreign body that diminishes the surface tension of the droplet, the for-

eign body becomes surrounded by the "artificial ameba." Such phenomena have been produced by a variety of methods. If a drop of mercury be placed in a dish of water rendered acid with nitric acid, its surface tension can be changed by placing a crystal of potassium bichromate in its neighborhood. This local reduction of surface tension causes the mercury to send out a pseudopodium toward the crystal and to move toward it. Similarly when a drop of chloroform is suspended in water and a particle of shellac is brought into its immediate vicinity, the chloroform drop envelops the particle of shellac and eventually dissolves it. If shellac has been painted on a particle of glass, the latter is engulfed as before. After the shellac has been removed, however, the drop of chloroform casts out the "indigestible" particle of glass. All of these processes so closely resemble the chemotactic and phagocytic activities of leukocytes and of certain lower forms of life that it seems certain that these also are to a large extent governed by the phenomena of surface tension and solution.

Chemotaxis in Higher Animals

When suspensions of pus-producing cocci are injected into the tissues of an animal, they soon become surrounded by a zone of inflammation containing numerous polynuclear leukocytes. These leukocytes are attracted to the locality by positive chemotactic substances emanating from the cocci. Such positive chemotactic substances have been extracted from various bacteria, and collections of leukocytes have been produced by their injection. It has been demonstrated, furthermore, that not only bacterial extracts but a variety of other substances have the power of attracting leukocytes in the animal body. Among these are turpentine, croton oil, and certain vegetable proteins (aleuronat). Probably also the disintegration of tissue gives rise to substances having a positive chemotactic influence upon the polynuclear leukocytes.

Increase of Polynuclear Cells in Circulating Blood.—In addition to the local collection of polynuclear cells at the point of infection, there is often also an increase in the number of these cells in the circulating blood. This increase is believed to be due to the escape of positive chemotactic substances from the point of infection into the blood. There they attract leukocytes out of the tissues and particularly out of their place of formation, the bone marrow. From the latter region not only mature leukocytes enter the blood stream but there may also be an entrance of immature cells with relatively few nuclei and even of myelocytes (page 616). The signs of active regeneration seen in the bone marrow are due in part to this loss of cells.

Absence of Leukocytosis in Some Infections.—The polynuclear leukocytosis which is present in many infectious diseases can thus be

explained in a fairly satisfactory manner. Why it should be absent in other infections is less clear. Overwhelming infections with the pneumococcus, for example, may cause little or no leukocytosis, and the latter is usually absent in typhoid fever, influenza, and tuberculosis. That these organisms contain positive chemotactic substances has been demonstrated by the collection of leukocytes which follows their injection into the peritoneal cavities of animals. A strictly localized infection may possibly in some instances fail to discharge chemotactic substances into the blood, and an overwhelming dose may paralyze or damage the marrow cells rather than irritate them. In many cases, however, such as typhoid fever, the explanation for the absence of leukocytosis is not clear.

Animal Parasites and Eosinophilic Polynuclears.—Infections with various animal parasites not infrequently lead to a leukocytosis in which the predominating cells are the eosinophilic polynuclears. Apparently these parasites exert a chemotactic effect upon this variety of cells, which is similar to the chemotactic effect exerted by bacteria upon the polynuclear neutrophils.

Phagocytosis in Higher Animals

When a purulent peritoneal exudate, produced by the injection of cocci, is examined microscopically, it is seen that many of the bacteria have been ingested by leukocytes that have collected in the region of the inflammation. These ingested cocci may show various stages of degeneration and disintegration. Even *in the milder types of infection* the leukocytes which contain many cocci may disintegrate but ultimately all cocci are taken up by the leukocytes and are destroyed. *In very severe infections* the phagocytosis may be quite active at first. Later, however, the disintegration of the leukocytes becomes more marked until finally the bacteria grow freely in the peritoneal exudate. It is evident, therefore, that a distinct relationship exists between the ultimate outcome of the infection and the degree of phagocytosis. Upon this fact is based the theory that the fate of the animal depends upon the result of the conflict between the infecting bacteria, on the one hand, and the phagocytic cells, on the other.

Metchnikoff's Macrophage and Microphage.—Particular attention has been paid thus far to the phagocytosis of bacteria by the polynuclear leukocytes, which are most active in the earlier stages of an inflammation induced by the injection of suspensions of cocci into the tissues. If later examinations are made, however, it is seen that a considerable number of large mononuclear cells have appeared in the zone of inflammation and that these are taking up particles of cellular detritus and even the polynuclear leukocytes themselves. Metchnikoff has spoken of these large mononuclear phagocytic cells as the macrophages, in contradistinction to the polynuclear leukocytes or microphages. The latter

seem to be particularly active in the ingestion of bacteria. The former ingest more particularly cellular detritus, extravasated red corpuscles, foreign bodies of various kinds and bacteria that produce chronic types of infection. It seems probable that cells of this type located in sinuses of the spleen, and to a lesser extent in the capillaries of the lymphatic glands, the bone marrow and the liver (Kuppfer's cells), normally remove from the circulation decrepit red corpuscles and finely divided particles of various kinds. These macrophages seem to arise from fixed cells of the tissues and are of connective tissue origin. Cells of similar appearance take up foreign particles in the lungs and these "dust cells" probably arise from the lining of the pulmonary alveoli. From the standpoint of infection, the macrophages are of particular importance in the later stages of the infection when they serve to remove the accumulated detritus as well as some of the bacteria. In certain types of infection and particularly in chronic infections, such as leprosy, they seem to play a more direct part by engulfing the bacteria.

Relation of Phagocytosis to Immunity

We have seen that, in certain instances, the severity of the infection and its probable outcome may be correlated with the degree of phagocytosis which takes place in the infected area. In discussing the relation of bacteriolysis to immunity, it was also pointed out that the phenomenon of bacteriolysis could not account for all types of immunity (page 522). This has been particularly exemplified in the case of infections with anthrax bacilli. Metchnikoff showed that no definite relationship exists between natural resistance to anthrax infections and the bactericidal properties of the blood serum. Rabbit serum has a greater bactericidal effect upon anthrax bacilli than has dog serum; yet rabbits are very susceptible to the natural infection, whereas dogs are highly resistant. On the other hand, there is a close parallelism between the phagocytic activities of the leukocytes and the natural resistance to anthrax. Thus in frogs, chickens, and dogs, all naturally resistant to anthrax, there is an active phagocytosis if the bacilli are injected into these animals; whereas in rabbits and guinea-pigs, both highly susceptible, no marked phagocytosis occurs. Similar relationships between phagocytosis and immunity have also been found for streptococci, staphylococci and pneumococci. Furthermore, animals artificially immunized against these infections show a definite increase in the phagocytic activities of their leukocytes.

Objections have been raised to these experiments by those who have supported the humoral theory of immunity. Possibly the bacteria are first killed by the fluids of the body and the phagocytes act simply as scavengers, which remove the bodies of the dead bacteria and do not carry on an active fight against the disease. The numerous experiments

that have been performed to settle this question have demonstrated fairly conclusively that leukocytes ingest living as well as dead bacteria, and that after ingestion the living bacteria may be killed. This fact, together with the intimate relationship that exists between the degree of phagocytosis and the degree of natural or acquired immunity to certain infections, leaves little doubt but that phagocytosis plays an important part in protecting against many infections.

Metchnikoff has, however, gone much further and has opposed the entire humoral doctrine of immunity, claiming that all types of immunity depend solely upon the activity of the cells in the body. We have already expressed the view that the bactericidal properties of the blood serum, whether natural or acquired, are not due to changes that occur after the blood has been drawn but that they exist in the unchanged body fluids. If this be admitted one must certainly assign to the bactericidal properties of the body fluids some rôle in the protection against infection. The degree of this protection becomes a quantitative rather than a qualitative question and must be decided separately for each infection. Naturally, in the last analysis, the bactericidal substances are derived from the body cells, but that they come solely from the polynuclear leukocytes or that they are directly connected with phagocytosis is more than doubtful. Furthermore, we now know that the phagocytic activity of the leukocytes is governed in large measure by substances present in the body fluids (opsonins). It is evident, therefore, that no sharp line of demarkation can be drawn between humoral and cellular processes in immunity reactions.

Types of Antibacterial Immunity.—It would appear, therefore, that antibacterial as opposed to antitoxic immunity may be due either to bactericidal substances in the body fluids or to the phagocytic activities of the leukocytes and other cells in the body, or to combinations of these two protective mechanisms. The rôle played by each differs in different infections. Immunity to typhoid, cholera and related infections is intimately associated with an increase in the bactericidal properties of the body fluids. Immunity to anthrax and to the pathogenic cocci, on the other hand, probably depends mainly upon active phagocytosis. The exact quantitative rôle which each plays in different infections is more or less undetermined at the present time.

The Opsonins

The increased phagocytosis, so frequently observed in animals that are naturally or artificially immune against an infection, was at first believed to depend upon changes in the activity of the leukocytes themselves. While the ability to perform phagocytosis undoubtedly does depend to some extent upon the activity of the cells, nevertheless the main

cause of variations in phagocytosis is a difference in the composition of the blood serum. Leukocytes from a non-immune animal, for example, show a certain degree of phagocytic activity when they are left in their own serum, but they become more actively phagocytic when placed in the serum of an immune animal. Further analysis of this phenomenon showed that washed leukocytes possess but little phagocytic activity against freshly cultivated bacteria. If, however, the bacteria are left in contact with immune serum and then separated by centrifugalization, they are readily taken up by washed leukocytes. Evidently the bacteria have absorbed from the serum certain substances which render them susceptible to phagocytosis. To these substances Wright has given the name of opsonins.

Opsonins in Normal and Immune Sera.—Opsonins are present in normal sera and they are increased in the sera of immunized animals, the increase being strictly specific for the microörganisms used during the immunization. Furthermore, according to Hektoen, there is during favorable cases of pneumonia a wavelike increase in the pneumococcus opsonins which reaches its height at the time of the crisis, whereas during fatal cases no such increase is demonstrable.

Concerning the structure of opsonins various views have been held. After a careful analysis of the available evidence, Zinsser came to the conclusion that "the full opsonic action both of normal and immune sera is dependent upon the coöperation of two bodies," one of which is comparable to the amboceptor that takes part in bacteriolysis, while the other is comparable to the complement. Whether or not the substances which prepare bacteria for phagocytosis are identical with the bacteriolytic constituents of the serum is at the present time an open question.

We thus see that the immunity due to phagocytosis is not a cellular immunity in the strict sense of the term, but that it is determined in large measure by the opsonins present in the body fluids.

Bacterial Resistance to Phagocytosis

Numerous studies have demonstrated that there is not infrequently a definite parallelism between the virulence of certain bacteria and their resistance to phagocytosis. Avirulent strains are readily engulfed by the leukocytes, whereas virulent strains resist phagocytosis. When virulence has been produced by passage through the animal body the associated resistance to phagocytosis, like the increased resistance to the agglutinative and bactericidal properties of the serum, indicates that the bacteria have developed a defensive mechanism against the attacks of the host. They have become "serum fast." For this reason the bacteria are able to maintain themselves in the body of the host, and upon this ability their virulence in large measure depends (page 500).

Causes of Increased Bacterial Resistance to Phagocytosis.—The exact cause of this increased resistance to phagocytosis is not well understood. Bail's view, that virulent bacteria secrete a substance which prevents the approach of the leukocytes, has not received general confirmation. Rosenow found that virulent, in contradistinction to avirulent pneumococci, failed to absorb opsonins from the serum. He found, furthermore, that a substance, virulin, could be extracted from the bodies of virulent pneumococci which had the property of neutralizing the opsonins of the blood serum. We have pointed out elsewhere that changes in virulence may be associated with changes in the exterior layers of infectious organisms. Capsulated strains of pneumococci and streptococci are in general more virulent than uncapsulated strains, and virulent colon bacilli may appear thicker than avirulent bacilli. This change in the exterior of bacteria may well bear a relation either to the absorption of opsonins or to their neutralization, but the exact mechanism in the different cases is still a subject of discussion.

Anaphylaxis and Protein Sensitization

Proteins taken in the food are absorbed by the mucous membrane of the intestines only after they have been broken down by the action of the digestive juices into relatively simple compounds, the polypeptids and amino acids. After their absorption, these compounds are again built up into proteins; but the latter, as we have learned from precipitin and other biological reactions, are to a high degree specific for each animal species. When proteins are introduced into the body by other routes than the digestive tract, i. e., parenterally, they are not prepared for the body by alimentary digestion and subsequent synthesis, but come directly in contact with the cells of the body. The first injection of a foreign protein ordinarily causes no physiological disturbance. That a change has occurred in the animal, however, is evident from the fact that a second injection of the same protein given after a suitable interval may produce manifest or even dangerous symptoms. The first injection is said to have made the animal sensitive to the particular protein used, and this condition of hypersensitiveness is spoken of as anaphylaxis.

The Sensitizing Dose. — It is evident that the phenomena described may be analyzed into three components: (1) the introduction of the sensitizing dose; (2) the period of incubation; and (3) the introduction of the second or toxic dose. Various protein substances have been successfully used in sensitizing animals. It seems probable also that no substances other than those of a protein nature are capable of inducing sensitization. The quantity of protein that must be introduced in order to produce sensitization varies considerably with different species

of animals. The guinea-pig may be sensitized by very minute quantities. Thus Rosenau and Anderson were able to sensitize guinea-pigs by injecting 0.000,001 c.c. of horse serum, while doses of 0.01 c.c. are commonly employed for this purpose. In most experiments the animals have been sensitized by injecting the foreign protein into the blood, the peritoneal cavity or the subcutaneous tissues. Sensitization may, however, be produced in other ways. For example, it may be transmitted from the mother guinea-pig to her young. Guinea-pigs have also been sensitized by being fed horse serum, by instillation of horse serum into the conjunctival sac, by inhalation of horse serum sprays, by keeping them in horse stables, and finally by inunctions of horse serum ointments. These experiments are of particular interest in view of the fact that human individuals are sometimes highly sensitive to foreign proteins, even though no injection of such proteins has ever been given.

Incubation Period.—A certain time must elapse after introducing the sensitizing dose before the animal reacts to a second injection of the foreign protein. This incubation period varies from about one to three weeks in different animals and under different experimental conditions. Once developed, the hypersensitive condition persists for a variable period of time. In the guinea-pig and in man it usually lasts for years, whereas in the dog and the rabbit it may disappear after weeks or months.

The Toxic Dose.—The symptoms produced by the second or toxic dose differ according to the animal used, but they are fairly constant for a given species of animal no matter what proteins have been used for the injections. The dose required to produce toxic symptoms is in general much larger than the dose required to produce sensitization, being for the guinea-pig from 200 to 2,000 times as large.

Specificity of Anaphylaxis

As a rule the injection of a foreign protein into an animal sensitizes it to the particular protein used and not to others. A guinea-pig, for example, that has received an injection of horse serum, is sensitized to subsequent injections of horse serum but is not affected by injections of rabbit or goat serum. Like all immune reactions, however, the specificity is relative rather than absolute and the sera of animals of close biological relationship, such as the chicken and the duck, may give rise to cross sensitization. Wells and Osborne also showed that cross sensitization could be produced between gliadin, the protein from wheat, and hordein, the protein from barley; although the crossed reactions were not so marked as when the same protein was used for the second injection.

Species and Organ Specificity.—In discussing the specificity of precipitins (page 528), it was pointed out that this biological reaction indicates that there is a more intimate biological relationship between the

various proteins derived from different organs of a given species of animals, than between proteins derived from the same organ of different species. The same rule holds with respect to the specificity of anaphylactic reactions. Extracts from various organs from a given species of animals produce crossed sensitization, whereas the extract from a given organ does not sensitize to the proteins of the same organ of a different animal species. The most noteworthy exception to this rule both in anaphylactic and in precipitin reactions is the protein from the crystalline lens which sensitizes to the lens proteins of different animals, but not to proteins derived from other organs of the same animal. Proteins from each organ also seem to show a certain amount of "organ specificity," for the treated animals are somewhat more sensitive to extracts of the same organ than to extracts made from other organs of the same animal.

Anaphylactic Reactions in Different Animals

Thus far we have spoken of the anaphylactic reaction in general terms without describing its physiological manifestations. These manifestations differ so markedly among different species of animals that no single description will apply to all cases. The physiological changes have been studied particularly in the guinea-pig, the rabbit, and the dog; but the diverse character of the reaction in these animals suggests that still further variations are possible in other animals.

(a) The Guinea-pig

After a guinea-pig, previously sensitized, has received an intravenous injection of a foreign protein, it remains quiet for about a minute. It then becomes restless, its hair becomes ruffled, it sneezes and rubs its nose. Within a few minutes it falls over and convulsions may occur. Soon respiratory difficulties appear and finally respiration ceases while the heart is still beating. At autopsy the lungs are found to be markedly distended and they do not collapse even when taken out of the body and cut into pieces. Auer and Lewis showed that this remarkable change in the lungs is due to a spasmodic closure of the finer bronchioles which finally causes the death of the animal from asphyxia. As in other conditions of bronchial obstruction this causes pulmonary distention.

(b) The Rabbit

Anaphylactic reactions are not obtained as regularly in the rabbit as in the guinea-pig. Two types have been described. The *local reaction* which occurs about repeated subcutaneous injections constitutes the so-called Arthus phenomenon. This local reaction consists in a local edema with infiltration which may persist for days or weeks. In very severe cases it leads to a local gangrene. The *general reaction* is obtained in only a

ig. 116.—Typical Anaphylactic Lung in the Guinea-pig (Right) Compared with Collapsed Lung (Left). Both Taken from Sensitized Animals After a Second Injection of Horse Serum. The Animal With the Collapsed Lung, However, Had Received a Dose of Atropin Before Being Given the Second Injection of Serum. (From Auer, Forchheimer's "Therapeusis of Internal Diseases.")

mall proportion of sensitized animals and then only when the toxic njection is given intravenously. After a preliminary quickening of the espiration the animal falls down with convulsive movements. Following the convulsions the animal lies motionless without breathing and alpation of the chest shows no cardiac movements. Acute distention of he lungs is usually absent in the rabbit. According to Auer, the cause f death is cardiac failure, for the heart shows both physiological and natomical changes. To what extent a vascular dilatation may contribute o the circulatory failure is uncertain. If the rabbit survive the acute ymptoms it may die later of cachexia. In this particular also it differs rom the guinea-pig, for the latter animal either dies or makes a good ecovery.

(c) The Dog

If a sensitized dog be given an intravenous injection of protein there s at first a short period of excitement which is soon followed by a proound depression with weakness and vomiting. In this stage the animal nay die or it may recover. There are no marked respiratory changes as n the guinea-pig and the cardiac changes observed in the rabbit are light or absent. Anaphylactic shock in the dog is associated with a

profound fall in the blood pressure, which reaches its lowest point about two minutes after the injection and only gradually returns to the normal. This fall in blood pressure is due to a dilatation of the blood vessels, especially in the splanchnic area, with a collection of blood in the abdominal veins and in the liver.

Summary of Typical Reactions.—It is evident, therefore, that the same cause, viz., the reinjection of a foreign protein, produces a different set of physiological reactions in each of these animals. In the guinea-pig, acute anaphylactic death is due to a spasm of the bronchial musculature; in the rabbit, intravenous injections may cause anatomical and functional changes in the heart, and subcutaneous injections may cause a marked local reaction; finally, in the dog, intravenous injections produce a marked fall of blood pressure which depends upon changes in the blood vessels rather than in the heart.

Other Changes During the Reaction. — Various other physiological changes occur during the anaphylactic reaction in animals. Thus the isolated virgin uterus of a guinea-pig sensitized to horse serum contracts when a minute amount of horse serum is added to the liquid in which it is suspended. Intestinal peristalsis is often markedly increased during anaphylactic shock. In the dog, the liver seems to play an important part both in the sensitization of the animal and in the production of anaphylactic shock, for if the liver be excluded from the circulation by an Eck fistula no fall of blood pressure results from the second injection of the protein, and no reaction whatever occurs if the liver has been excluded from the circulation previous to the sensitizing dose. The dog's blood becomes less coagulable during the height of the anaphylactic shock and at the same time the polynuclear leukocytes practically disappear from the circulating blood. As the animal recovers a polynuclear leukocytosis appears. Mild or delayed reactions may cause an eosinophilic leukocytosis in the dog and guinea-pig. There is also a local eosinophilia in the lungs of guinea-pigs and in the subcutaneous edema of rabbits who show the Arthus phenomenon. Subacute anaphylactic shock may give rise to an acute fall of the body temperature. When still smaller toxic doses are used fever may be produced.

Passive Anaphylaxis

If the serum of an animal sensitized against a particular protein be injected into another non-sensitive animal, the latter may become sensitive to the protein used. It is possible, therefore, to transfer the anaphylactic condition from one animal to another by means of the blood serum. The conditions governing such a transfer are, however, but imperfectly understood. In many experiments the animal which receives the transfer is not immediately sensitized but becomes so in a few hours or in a day or

two. Apparently the injected serum must react in some way with the body cells of the recipient. In other experiments the sensitization seems to have occurred immediately. Poisons which produce physiological effects similar to the anaphylactic reaction have been prepared by allowing the blood serum of a sensitized animal to act upon its specific protein.

Antianaphylaxis

After an animal has recovered from an anaphylactic shock, it is for the time being refractory to doses of the foreign protein which would otherwise be surely fatal. This refractory condition usually lasts only a few days or at the most a few weeks, and it may be followed by a period of moderate hypersensitiveness.

Theory of Anaphylaxis

At first appearance anaphylaxis seems the antithesis of immunity. The treated animal, instead of being less sensitive to the action of a particular protein (prophylactic action), becomes more sensitive (anaphylactic action). Yet anaphylaxis, so strikingly different from immunity in its physiological manifestations, is beyond doubt intimately related to immunity, and its study has thrown a flood of light upon the nature of infection. Unfortunately, at the present time our knowledge of the anaphylactic phenomena is in many ways fragmentary and the problems involved are of great complexity, so that no theory of anaphylaxis can be said to be definitely established. We shall, therefore, content ourselves with a brief presentation of the two main theories that have been advanced. According to the first of these, the toxic substance (anaphylotoxin) is derived from the foreign proteid injected. According to the second, it is derived from an autodigestion of the animal's blood serum.

First Hypothesis. — Vaughan has shown that when proteins of bacterial, vegetable or animal origin are exposed to the action of weak alkalis dissolved in absolute alcohol, they are split into two classes of substances, the one poisonous and the other non-poisonous. The former, irrespective of their origin, produce a constant physiological action. Biologically they neither sensitize nor lead to the formation of antitoxins. The latter, or non-toxic group of substances, differ among themselves in their biological reactions. Vaughan conceives that when a foreign protein is introduced parenterally into the animal body it is digested by cellular ferments which split it up into these two groups, the toxic and the non-toxic. In previously untreated animals the amount of ferment available for this purpose is small and consequently the digestion of the foreign protein takes place slowly. The toxic group, therefore, is not liberated with sufficient rapidity to cause manifest physiological disturbances. In consequence of such an injection, however, the cells of the

body are stimulated to form large quantities of the specific ferment which digests the particular protein introduced. When this foreign protein is reinjected after a sufficient interval of time, the specific ferment, now greatly increased in amount, splits up the protein very rapidly into its component parts and the toxic portion thus liberated causes the marked physiological effects which characterize anaphylactic shock. According to Vaughan's theory, therefore, anaphylactic shock in a given animal is the same no matter what proteins are used, for the reason that the toxic portions of different proteins have the same physiological action. The specificity of the reaction which requires that the same protein must be used both for the sensitizing and for toxic doses is explained on the assumption, that each protein requires a specific ferment for its digestion and the primary injection stimulates the cells to the formation of this ferment and of no other. It is unnecessary to point out that such specific responses on the part of the body cells are well known in other fields of immunology.

Character of Substance Arising from First Injection.—Whether the specific substance produced in response to the first injection is a ferment, as Vaughan believes, or whether it acts more as an amboceptor that assists ferments already present in the body to attack the foreign protein (Friedberger), is still under discussion. Considerable evidence has been adduced in favor of the latter view and it has been shown, in particular, that anaphylactic shock is associated with a marked reduction of the complement of the blood.

Second Hypothesis.—According to the hypothesis just advanced, the phenomena of anaphylactic shock are due to the formation of toxic substances in consequence of a rapid digestion of the foreign protein that was injected into the animal. It has been shown, however, that the blood serum may be made toxic by adding a variety of chemically inert substances, such as agar, starch or kaolin suspensions; and Novy has produced the typical manifestations of anaphylactic shock by the single injection of a non-protein material, such as a dilute agar solution. The effects produced in this manner apparently depend upon the colloidal character of the solution used and they appear to be due to an autodigestion of the blood plasma itself by ferments which are set free in consequence of colloidal changes in the plasma. Bronfenbrenner assumes, for example, that the foreign substance removes antitrypsin from the blood by a process of absorption. The blood trypsin then digests the blood proteins and in this manner gives rise to toxic substances.

The specific effects produced by the second injection of a foreign protein may be readily explained on this hypothesis. As a result of the first injection various antibodies are formed, among which are the precipitins. When the second injection is given, the foreign protein combines with its specific precipitin, and as a result of this combination a

colloidal precipitate is formed which acts in a manner similar to the agar solution. Proteolytic ferments are set free and these rapidly digest the proteins of the blood. In this way toxic substances are formed which cause the anaphylactic shock.

Anaphylactic Shock an Immunity Reaction.—Whichever theory be adopted, the anaphylactic shock produced by a second injection of a foreign protein appears to be closely related to the biological reactions that characterize the development of immunity. If the first theory be adopted, the rapid digestion of the foreign protein may be compared with the destructive action which immune blood exerts upon foreign cells and bacteria. If the second theory be adopted, anaphylaxis depends upon a reaction between specific precipitins and their antigens. That the reaction between the foreign protein and these immune bodies may under the conditions of this experiment do great harm is highly important from the practical standpoint. Nevertheless, from the standpoint of immunity reactions it is incidental and does not constitute a fundamentally different reaction from those which under other conditions produce an increased resistance on the part of the animal.

Relative Part Played by the Body Cells and Fluids.—That anaphylactic phenomena may occur in the absence of the body fluids has been proved by the experiments of Schultz and of Dale. The latter, for example, showed that the uterus of a sensitized animal when washed free of blood and placed in Ringer's solution exhibits a typical anaphylactic response if the protein used in sensitization be added to the surrounding solution. In favor of the view that an anaphylactic phenomenon may depend, in part at least, upon the fluids of the body is the fact that it may be transferred passively from one animal to another by serum injections. It is probable, indeed, that both the body cells and the body fluids play a part in rendering the animal susceptible to future injections of the protein. As in other biological reactions the specific substances are formed by the cells of the body and are cast off by them into the fluids. The fact is not surprising, therefore, that, under certain experimental conditions, hypersusceptibility has been shown to reside in the cells of the body while, under other conditions, it has been demonstrated in the body fluids.

Protein Hypersensitiveness in Man

(a) Serum Diseases

The use of various sera in the treatment of human disease soon led to the discovery that such injections were not infrequently followed by undesirable symptoms, the most common of which were rashes of an urticarial type. That these symptoms depended upon the serum used

and not upon the specific antibodies contained therein is well established, for they occur not only after injections of antidiphtheritic, antistreptococcic sera, etc., but also after injections of serum derived from normal horses. Furthermore, there is a direct relationship between the amount of serum used and the incidence of symptoms. This is apparent in the following table taken from Weaver's statistics:

Incidence of Serum Disease Arranged According to Amounts Given

Total amount of serum	1–9 c.c.	10–19 c.c.	20–29	30–49	50–99	100 or over
Total number of cases	82	189	140	120	121	40
Cases showing reaction	9	52	40	47	61	27
Percentage showing reaction	10.9	27.5	28.5	39.2	50.4	67.5

The use of sera with high antitoxic content diminishes the incidence of serum disease, for less serum is then necessary in order to administer the requisite number of antitoxin units. Sera also vary among themselves, for the sera from certain horses produce undesirable symptoms more frequently than equal amounts of sera derived from other horses. Finally, the tendency of horse serum to produce toxic symptoms seems to diminish as the serum ages. For this reason manufacturers ordinarily keep their therapeutic sera on ice for some time before placing them upon the market.

Reactions After Injection of Horse Serum.—The typical reaction which follows a first injection of horse serum into man does not develop until about the eighth or ninth day after the injection. Among the manifestations are skin rashes of an urticarial or erythematous character, fever, malaise, glandular swellings, joint and other pains, edema, and occasionally albuminuria. These symptoms last from a few days to two weeks and recovery practically always takes place. Von Pirquet and Schick pointed out that when an individual had received injections of horse serum on previous occasions, this *typical first reaction* was modified, and they described two types of modified reaction. The first of these, or the *immediate reaction*, occurs within the first twenty-four hours; the other, or the *accelerated reaction,* occurs on the fifth to the seventh day. Both are qualitatively similar to the reaction which may follow a first injection but both run a more rapid course. When the reinjection is given in from ten days to six months after the primary injection the immediate reaction is more apt to appear; after six months the accelerated reaction is the more common; combinations of the two are also not infrequent. Furthermore, reinjections of horse serum, unlike the primary injection, not infrequently produce a marked local infiltration about the point of injection. This local reaction is similar to that which has been observed when rabbits are given repeated injections of horse serum (Arthus phenomenon).

Dangerous Symptoms After Injection.—Occasionally the injection of horse serum into man is shortly followed by a series of alarming

and dangerous symptoms. In a case reported by Gillette, for example, the patient, who was subject to asthma, asked for an injection of diphtheria antitoxin in the hope that this might cure his disease. He received 2,000 units. While dressing he experienced a prickling sensation in the neck and chest. Soon he sat down and complained that he could not breathe, nor did he breathe again. The pulse at the wrist remained regular and full for some time after respirations ceased. Death apparently occurred from asphyxia. Fortunately such accidents are very rare. They have occurred more frequently after first than after later injections of the serum. The resemblance to anaphylactic shock in the guinea-pig is a striking one and the view that death, like that of the guinea-pig, depends upon an acute spasm of the bronchial muscles is supported both by the observation that in some cases there has been an acute distention of the lungs, and by the fact that most of those who have suffered from such symptoms have been sufferers from asthma or other respiratory affections. The dangers attending serum injections into such patients, and particularly in those who are sensitive to contact with horses (horse-asthma), must always be borne in mind when antitoxin is administered. In other patients the acute symptoms following injections of horse serum have suggested a circulatory collapse, and it is possible that such a collapse may occur either from involvement of the heart, as in rabbits, or from involvement of the vascular apparatus, as in dogs.

Manner of Sensitization.—One remarkable feature of these acute deaths is the fact that not a few of the individuals affected have never received a previous injection of horse serum. One might assume that in such patients the horse serum acted as a primary poison and that there was no relation to the anaphylaxis observed in animals. However, the general resemblance to the anaphylactic shock of guinea-pigs, and the fact that human individuals are not infrequently hypersensitive to other protein substances, even though they have never received injections, indicate that hypersensitiveness in man may result in some other manner than by the injection of the foreign protein. We know that guinea-pigs may be sensitized to horse serum by various other means, such as the feeding of horse serum, inhalations, enemata, and inunctions, and it is probable that the same is true of man. There is, indeed, direct evidence that foreign proteins may at times enter the blood in an unchanged condition from the intestines, particularly in infants and during gastro-intestinal disturbances, for under certain conditions the foreign protein has been demonstrated by biological methods both in the blood and in the urine. There is also reason to believe that foreign proteins may be absorbed unchanged by the respiratory tract, particularly in hay fever. It seems probable, therefore, that the acute deaths which result from a first injection of horse serum are due, not to a primary toxicity of the serum but to an anaphylactic condition of the individual, which

has resulted from a previous absorption of unchanged horse protein by the intestinal tract, or in some other way.

(b) Hay Fever

It has long been known that certain individuals develop the symptoms of coryza during definite periods of the year, a fact which has given rise to the terms June cold (rose cold, summer catarrh) and autumnal catarrh. Summer catarrh is produced by the pollen of various grasses (graminaceæ), among which are the foxtail, timothy, rye, and wheat. Autumnal catarrh is produced by the pollen of various compositæ, and particularly of the ragweed and goldenrod. Individuals suffering from the pollen of one group are usually sensitive to all members of this group, but are unaffected by members of the other group. Attacks of hay fever may be induced artificially at any time of the year by instillating into the conjunctival sac suspensions of the pollen or solutions containing the pollen proteins. When such solutions or suspensions are placed upon the abraded skin they give rise to local urticarial eruptions. Dunbar injected a small amount of the protein solution into the forearm of his associate, Praussnitz, who was a sufferer from hay fever. The results were alarming but instructive. In about ten minutes a severe coryza developed, which was accompanied by swelling of the conjunctivae and chemosis. An hour later the patient began to suffer from a severe attack of asthma. The forearm that had received the injection became markedly swollen and this swelling extended later over the entire arm. For a week after the injection, Praussnitz felt weak and exhausted. Similar injections into individuals who had never suffered from hay fever produced no effect other than a slight itching edema about the point of injection.

Pathogenesis.—Koessler believes that normal individuals protect themselves against the pollen that falls upon their respiratory surfaces at certain seasons of the year by digesting these slowly without absorption. The patient with hay fever, on the other hand, has become hypersensitive by absorption of the pollen protein. Thereafter the sensitized cells of the respiratory passages absorb and digest the protein very rapidly, and the toxic products that are set free produce a local inflammation or general symptoms. A relatively serious form of pollen intoxication is hay-asthma. This is due either to a local action of the pollen proteins upon the bronchi or to the passage of the protein or its toxic constituents into the body fluids of a sensitive individual.

(c) Sensitization to Other Proteins

Various other types of protein sensitization have been described, such as that to eggs, to buckwheat flour, to shell-fish, and to contact with horses,

cats, or guinea-pigs. The writer knows of individuals who are sensitive to mustard and to glue, and the list could doubtlessly be lengthened considerably. The manifestations of such a sensitization may be local or general. When the offending protein is dropped into the conjunctival sac the mucous membrane may become inflammed and swollen. When it is placed on the abraded skin a local inflammation or urticarial wheals may result. An injection into the subcutaneous tissues may be followed by an infiltration similar to the Arthus phenomenon. Among the more common clinical manifestations of protein sensitization in man are gastro-intestinal disturbances, asthma and skin rashes. The last are commonly of an urticarial or erythematous character, and they occur particularly after the offending material has been absorbed from the alimentary tract.

Asthma and Protein Hypersensitiveness.—Asthmatic seizures may result when material containing the protein is inhaled. This is the case in hay-asthma and in horse-asthma, in which conditions the paroxysms are precipitated by contact with pollen or with horses. The injection of horse serum into this latter class of individuals is accompanied by unusual dangers, and some of the sudden deaths after injections of antitoxic sera have occurred in subjects of horse-asthma. Asthmatic symptoms may also develop when the protein is injected subcutaneously or when, as in egg-asthma, it is eaten. It is possible, indeed, that all cases of asthma are due to protein hypersensitiveness, and that the frequent association of asthma with infections of the respiratory passages is due to the development of hypersensitiveness on the part of the patient toward the proteins of the infecting organisms (page 378).

(*d*) Hypersensitiveness to Bacterial Proteins

The introduction of bacterial proteins into the body may sensitize the individual to these proteins. Typical anaphylactic shock has been produced in various animals by the reinjection of bacteria, dead or alive, and by the injection of bacterial extracts. During or after certain infectious diseases of man the patient is hypersensitive to products derived from the infecting microörganisms. As examples of such bacterial sensitization one may mention the various tuberculin reactions, the gonococcus reaction of Irons, the typhoid reactions of Chantemesse and of Gay and possibly the luetin reaction of Noguchi.

The Tuberculin Reaction

Of these the most widely used and best studied is the tuberculin reaction. In tuberculous patients *local reactions* at the point of application may occur when tuberculin is applied to the scarified skin (von Pirquet test), when tuberculin solutions are dropped into the conjunctival sac (Calmette reaction), when tuberculin ointment is rubbed on the unbroken

skin (Moro reaction), or when tuberculin is injected cutaneously or subcutaneously. The absorption of tuberculin, particularly after a subcutaneous injection, gives rise to the so-called *general reaction* which is characterized by fever lasting a few days with the usual accompanying symptoms. The focus of disease in the body may show evidences of increased inflammation. For example, areas of lupus vulgaris become red and swollen, tuberculous joints enlarge and become more painful, and tuberculous lesions in the lungs may show more numerous râles with an increase of sputum. These constitute the *focal reaction.*

Significance of a Positive Reaction.—The significance of a positive tuberculin reaction has been much discussed. It is now generally held that such a test always indicates an infection with tubercle bacilli. This does not mean, however, that tuberculosis in the clinical sense is present, for the reaction is frequently obtained in individuals who present no clinical manifestations of tuberculosis, and who do not develop the disease at later periods of life. Von Pirquet showed that the number of children with a positive cutaneous test increases progressively with advancing years. His figures are as follows:

Cutaneous Tuberculin Reactions in Children Arranged According to Age

Age	Months			Years					
	0–3	3–6	5–12	1–2	2–4	4–6	6–10	10–14	over 14
Per cent of positive reactions	0	5	6	24	37	53	57	58	90

Others have obtained a smaller proportion of positive reactions in adults, owing doubtlessly to the lesser prevalence of tuberculosis among the particular group of individuals studied. Among the students in the Medical Department of the University of Michigan, for example, it was found that only about one-third gave positive cutaneous tests. Similar results have been obtained when tuberculin has been injected subcutaneously into supposedly healthy individuals. Hamman and Wolman, for example, estimate from their own experience, as well as from the experience of others, that approximately 50 per cent of apparently healthy individuals give tuberculin reactions after subcutaneous injections. It is evident, therefore, that a considerable proportion of all individuals give positive cutaneous and subcutaneous tuberculin tests. The tests indicate, as autopsy records have shown, that a large number of people have at some time become infected with tubercle bacilli without necessarily developing noteworthy clinical manifestations. It is not our purpose to discuss the diagnostic value of tuberculin reactions, but it may be pointed out that, aside from the reaction at the focus of infection, no very fixed relationship exists between a positive tuberculin test and the clinical manifestations of the disease. In a general way the reactions are more common and more

severe in those showing clinical evidence of the disease, but the numerous exceptions to this rule make it difficult to interpret the reaction in any particular case.

EFFECT OF TUBERCULIN ON NORMAL INDIVIDUAL.—Whether or not the injection or application of tuberculin will sensitize a normal non-tuberculous individual in such a manner that he will subsequently give a positive tuberculin reaction is still an open question. It is well known that a second instillation of diluted tuberculin into the conjunctival sac frequently produces a reaction when the first instillation had been without effect, and it is often assumed that the conjunctiva has been sensitized by the first instillation, and that this may occur even in individuals who are free of all tuberculous infections. Experiments have shown, however, that it is extremely difficult, if not impossible, to induce positive tuberculin reactions in normal animals by repeated injections of tuberculin. The only effect produced is anaphylactic shock. On the other hand, animals that have been treated with living or dead tubercle bacilli will give a typical reaction when tuberculin is injected. It seems probable, therefore, that the hypersensitiveness to tuberculin which gives rise to the characteristic reaction is in some way associated with infection by the bacilli rather than with the absorption of tuberculin itself.

Some Phenomena of Infection

The general, as distinguished from the local, manifestations of infection may be divided into two classes. To the first belong the formation and the reactions of the various antibodies, such as antitoxins, bactericidins, bacteriolysins, agglutinins, opsonins, etc. These have been discussed in the preceding sections. To the second group belong the clinical manifestations, such as the changes in temperature, respiration, circulation and metabolism, the loss of appetite and the nervous symptoms. These are discussed, in part, under the appropriate headings, and more particularly in the chapter on fever. The manner in which infection produces certain of these clinical manifestations and their relation to anaphylactic symptoms will be discussed briefly in the following paragraphs.

Cause of Symptoms

Infections are caused by the growth of microörganisms in the tissues of the animal body. Aside from changes in the immediate neighborhood of the invaders, the symptoms of infection may be due: (1) to soluble toxins secreted by the invading microörganisms; (2) to poisonous substances liberated from the bodies of the dead bacteria; and (3) to substances derived from the tissues or fluids of the host.

(1) Soluble Toxins

Infections with bacteria that produce soluble toxins liberate these toxins in the body of the host, and the symptoms of the infection may be more or less dominated by the action of these poisonous substances. The nervous manifestations of tetanus and the nervous and cardiovascular disturbances of diphtheria, for example, correspond to the symptoms produced when the soluble toxins are injected into an animal. Soluble toxins have also been prepared from other microörganisms (page 512), but in most cases the symptoms of the corresponding infections cannot be accounted for in this manner.

(2) Substances Derived from Bacterial Disintegration

The great majority of infectious bacteria produce no soluble toxins, or at least none that can account for the major symptoms of the infections which they cause. It is an old view that such bacteria contain harmful substances which are liberated when the bacteria disintegrate in the body of the host. Pfeiffer conceived that such bacteria contain within themselves certain preformed poisonous substances, called endotoxins, which were specific for each organism, and which produced the characteristic manifestations of the infection. Vaughan, on the other hand, has held that the poisonous substances liberated are not specific, but that they are similar to those liberated when any foreign protein disintegrates within the animal body. He regards the symptoms of infection as being, in essence, those of a prolonged intoxication with the decomposition products of foreign proteins derived from the invading bacteria.

(3) Substances Derived from the Host

Fever may result from a disintegration of the fluids or tissues of the body itself (page 483), and it is not improbable that some manifestations of infection may be due to this cause. Indeed, according to one theory of anaphylaxis, the toxic action of reinjected proteins is due to colloidal changes in the body fluids which produce toxic substances from the body itself.

Whether the immediate cause of the toxic symptoms in anaphylaxis be substances derived from the foreign protein or substances derived from the normal body fluids, there are many analogies between infection and the effects produced by single or repeated injections of a foreign protein. In the following paragraphs particular attention will be directed to these analogies.

The Incubation Period

One of the characteristic features of infectious diseases is the interval that elapses between the entrance of the microörganisms and the subse-

quent development of symptoms. Analogies to this incubation period seen in protein intoxications. Thus we have seen that, in order to produce anaphylactic shock, a certain time must elapse between the first and the second injections of the foreign protein, during which time certain antibodies against the foreign protein are being developed within the body. Furthermore, after a first injection of horse serum into a human being, the symptoms of serum disease do not ordinarily develop until eight or nine days have passed. It is often assumed that the incubation period of an infectious disease depends upon a multiplication of the causative organisms in the body, but in serum disease no such multiplication can occur, and, in this case at least, the incubation period must be due to some other cause. According to von Pirquet, the incubation period of serum disease represents the time required for the body to elaborate the specific antibodies which react with the foreign proteins of the horse serum, and thus cause a liberation of the toxic substances that produce the symptoms.

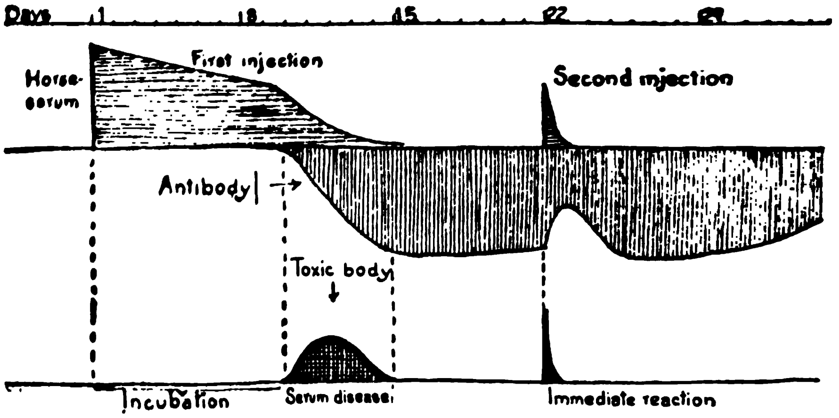

Fig. 118.—The Incubation Period in Serum Disease. When the Antibody to the Horse Has Formed the Two Interact and Give Rise to the Toxic Body Which Causes the Disease. A Second Injection, Given Shortly After, Causes an Immediate Reaction Because Antibody Is Already Present in the Blood. (From Pirquet, Arch. Int. Med.)

If a second injection of horse serum be given a few weeks after the first, there is an immediate reaction, because the serum encounters antibodies already formed in the body of the individual.

Incubation Periods of Infections.—Similar relations apparently hold with regard to certain infections. Thus Vaughan states that if a lethal dose of living colon bacilli be injected into the peritoneal cavity of a guinea-pig, the incubation period is from eight to twelve hours, if a lethal dose of the dead bacilli be injected the incubation period is shortened to about four hours, while if toxic products derived from colon bacilli be injected the animal dies almost immediately.

Importance of Infectious Incubation Period.—The incubation period of an infectious disease, therefore, while devoid of symptoms, is of

great importance from the standpoint of infection. Not only do the infecting organisms gain an entrance to and multiply in the body of the infected individual, but the latter is preparing the specific substances which later play a part in the conflict that characterizes the disease itself.

Anaphylactic Fever

During subacute anaphylaxsis the temperature of the animal frequently falls. In infectious diseases it usually rises. This discrepancy is apparent rather than real; for Vaughan as well as Friedberger has shown that it is possible to produce any type of fever by protein injections, provided sufficiently small doses be chosen and these be repeated at sufficiently frequent intervals. In other words, one must produce a gradual type of protein intoxication comparable to that present when foreign microörganisms disintegrate in the body. Furthermore, we know that a rise of temperature is not a necessary accompaniment of infection. When an individual with but little resistance suffers from a severe infection the body temperature may fall, causing the so-called febrile collapse. This fall of temperature finds its analogy in the lowered temperature of subacute anaphylaxsis.

Physiological Mechanism of Rise.—The physiological mechanism governing the rise of temperature in infectious fever and in that accompanying protein intoxication also appears to be the same. In the chapter on fever it was pointed out that the rise of temperature in fever is probably due to some disturbance in the heat regulatory centers of the midbrain. If these centers be cut off from the remainder of the body, the introduction of microörganisms does not cause a rise of temperature. Leschke has shown that the reintroduction of protein into animals operated upon in this manner also fails to affect the body temperature.

Circulatory Changes

We have seen (page 114) that the circulation in fever is frequently abnormal and that the circulatory collapse of infectious diseases, like the circulatory collapse in surgical shock, is probably due to a collection of blood in the veins of the abdomen owing to a loss of venous tone. It may be pointed out in this place that the circulatory changes which characterize anaphylactic shock in the dog are also accompanied by a collection of blood in the abdominal veins. The general analogy is a striking one, although it is not possible at the present time to affirm that the two are precisely the same.

Other Analogies Between Infection and Protein Intoxication

Infections are usually accompanied by some increase in the protein metabolism (page 475). Major found a similar increase in rabbits after

injections of horse serum. Finally, Longcope has shown that anatomical changes may be produced in the kidneys, the myocardium and liver by repeated injections of a foreign protein, and it is possible that the changes accompanying and following infections are also due in part to the effect of the disintegration of the bacterial proteins in the body.

The Specificity of Infections

The view that a single substance may be responsible for the general symptoms of infection is not a new one, but may be found throughout the earlier literature on fever. Opposed to this view has been the fact that each infectious disease tends to pursue a more or less characteristic course with involvement of certain organs in the body. These specific differences are due in part to differences in the portal of entry into the body and in part to the tendency of each invader to localize in certain tissues where they produce local as distinguished from general symptoms. Vaughan has pointed out, however, that a variation of toxic symptoms, when different proteins are used, may also occur, even though the immediate toxic agent be the same in all cases. Sensitization of the body is primarily cellular in character, and the tissues that are sensitized in different infections are probably different. As a result of these differences the foreign protein will be split up in greater quantity at certain points of the body, and the toxic action will therefore be greater at these points.

Chronic Intoxication Hypothesis of Infection.—Numerous analogies certainly exist between the symptoms commonly observed in infections and those which may be produced by repeated and properly spaced injections of a foreign protein. The conception of infection as a chronic intoxication, analogous to that which may be produced by repeated injections of any foreign protein, has thrown much light upon and has done much to stimulate interest in the nature of the physiological alterations in fever, and it will beyond doubt influence all future interpretations of the manifestations of infection. Nevertheless, it seems possible that there is a tendency at the present time to push the analogy between infection and protein intoxication too far, and that too little emphasis has been laid upon the specific differences between the various infections and the differences between infection and anaphylaxis. In this connection, it may be recalled that normal animals treated with tuberculin react to future injections only with anaphylactic shock, whereas animals who have the disease give a typical tuberculin reaction.

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Chapter XI

The Blood

Functions of the Blood

The blood is the common carrier of the body. It carries oxygen from the lungs to the tissues and carbon dioxid from the tissues to the lungs. It transports food to the organs and waste products to the kidneys. It contains the internal secretions and the complex biological substances which have to do with the processes of immunity and recovery from infections. These functions are discussed in other places. In the present chapter attention will be paid more particularly to variations in the quantity and concentration of the blood, to changes in its formed elements and to alterations of its coagulating properties.

The Quantity of Blood

Most of our data concerning the blood deal with the concentration of its various constituents in a unit of volume and not with the total amount of these constituents in the body. It is not easy to determine the total blood volume. The most accurate determinations are those made on animals by bleeding and then washing out the blood vessels (Welcher's method).

Bloodless Methods for Determining Volume.—Bloodless methods for determining the total volume of blood are based upon a single principle. A definite quantity of a known substance is added to the circulation and its concentration in a sample of blood is estimated shortly thereafter. If the substance added has not left the circulation and if it has caused no interchange of water between the blood and the tissues, it becomes possible to calculate the total quantity of blood in the body from the concentration of the foreign substance in a unit of blood volume. By this method, estimates of the total quantity of blood in the body have been made: (1) by injecting normal salt solution into the veins and then determining the dilu-

tion of the blood; (2) by inhaling a given amount of carbon monoxid and then determining the amount of carbon monoxid hemoglobin in the circulating blood; (3) by injecting a given amount of tétanus antitoxin intravenously and later determining its concentration in the serum; and (4) by introducing into the circulation a non-toxic, slowly absorbable dye (vital red). Of these the carbon monoxid method has been the most extensively used. Comparisons with Welcher's method have shown its essential accuracy. When used on animals, it gives somewhat higher figures than bloody methods, probably because the hemoglobin in the muscles take up a portion of the carbon monoxid. The injection of salt solution has yielded concordant results in the hands of certain investigators, although it would seem less reliable on account of the ease with which it leaves the blood vessels. The injection of vital red promises to be the simplest of the methods thus far used. According to these methods, the total quantity of blood in the human body normally constitutes from 5 to 8.8 per cent of its weight. Higher figures (10 per cent) have been obtained by the tetanus antitoxin method.

Maintenance of Blood Volume.—Experimental studies have shown that the blood volume is maintained with considerable persistence despite influences which tend to alter it. When a physiological salt solution is injected intravenously it passes out of the circulation quite rapidly, and this happens even though excretion through the kidneys be excluded. The extra fluid is taken up by the tissues. Even when blood is directly transfused from another animal of the same species it does not lead to a permanent increase in the amount of blood within the blood vessels. An increase of 80 per cent in the total quantity of blood can be received without serious symptoms and much larger quantities have been given. The immediate effect of such a transfusion is an increased fullness in the vessels of the mucous membranes and retina. The fluid portions of the blood are then rapidly eliminated from the blood vessels so that an increased concentration of cellular elements occurs. By such injections of blood the red cells may be increased to ten million or more per cubic millimeter, but the injected red cells disappear in from four to seven days, according to the number injected. In some cases, however, normal conditions are not reëstablished for 28 to 30 days. A continued increase of blood has been produced experimentally in rabbits by Hess, who injected defibrinated blood repeatedly into their blood vessels.

Reduction Difficult.—Attempts to reduce the volume of blood also meet with considerable difficulties. After a hemorrhage the volume of blood is rapidly restored by a passage of liquid from the tissues into the blood vessels. The extent to which this occurs obviously depends upon the amount of fluid available in the tissues and upon the amount which is taken by mouth. Rabbits, for example, are said to restore the original volume of blood within two or three hours after being bled to a third or

even a half of their total hemoglobin, while in dogs and men the restoration is more gradual.

Plethora

The doctrine of plethora or an increased amount of blood in the body played a very important rôle in the minds of physicians and pathologists half a century ago, and it derived therapeutic importance from the fact that it was considered an indication for bleeding. At autopsy an increased quantity of blood often seemed to be present in the body. According to these older views, plethora was suggested clinically by a full condition of the peripheral blood vessels with a tendency toward hyperemia of the visible mucous membranes and skin. It was supposed to be a cause of cardiac hypertrophy, and to predispose to congestions and to cerebral hemorrhage. Doubtlessly many of these "full-blooded" patients whose symptoms were formerly attributed to plethora belong to the group that we now recognize as chronic hypertention. Veith, Rowntree and Geraghty have shown, however, that plethora is not the rule in such patients.

Increase of Blood Volume.—The newer methods for estimating the quantity of blood in the body have shown that this quantity is at times definitely increased. In patients with polycythemia, for example, the total volume of blood may be normal or it may be increased, even to two or three times the usual amount. The blood volume is usually increased in chlorosis and it is occasionally increased in certain other anemias and in anasarca. During the later months of pregnancy a moderate increase of blood volume also occurs. Aside from this condition, however, simple plethora seems to be rare. The more marked increases in the total blood volume are associated either with qualitative changes in the blood itself or with manifest disease of other organs.

Oligemia

In contrast to the plethoric state a condition of oligemia or diminished quantity of blood is suggested when the patient is unusually pale, but the percentage of hemoglobin is normal. The skin pallor may, however, be due to a vascular constriction of the cutaneous vessels or possibly, as Sahli suggests, to some unusual thickness of the skin. No demonstration has been furnished that oligemia actually exists in such patients. Only in obesity is the blood volume small in proportion to the body weight.

From Depletion of Water.—It is recognized, however, that a reduction in the volume of blood in the body may be produced by a serious depletion of water, such as may occur, for example, in Asiatic cholera. Such oligemias are, as a rule, temporary, for when the diarrhea subsides and the increased thirst is satisfied the blood volume returns to the normal.

Hydremia

Hydremia means a watery condition of the blood. Since the corpuscular elements in the blood are relatively rich in solids, their number markedly influences the percentage of water in the total blood. It seems advisable, however, to exclude from consideration the changes in blood concentration that are caused by variations in the number of corpuscles. Thus restricted, the term hydremia means a watery condition of the blood serum or blood plasma. The degree of hydremia can be estimated by determining the total amount of solids in the blood serum or by determining its specific gravity. Variations in the solid constituents of the blood serum are due mainly to variations in the percentage of proteins present, for the concentration of sodium chlorid, its principal salt, is relatively fixed. A watery condition of the blood serum usually means, therefore, that the percentage of proteins is low. Only when there is a considerable accumulation of non-protein nitrogen in the blood do variations from this rule occur. The pereentage of proteins present in the blood can be approximately determined by estimating its refractive index. Since this estimation requires but little time and only small quantities of blood, it is the most convenient clinical method for determining the degree of hydremia.

Physiological Variations of Blood Concentration.—Repeated examinations of the refractive index of the same individual have shown that the concentration of the blood serum is subject to a number of physiological variations. Its concentration is increased after exercise; partly, perhaps, because of the perspiration, but mainly because the exercised muscles take up water. It is diminished immediately after bleeding on account of the dilution of the blood with lymph, which is relatively poor in proteins. It is diminished for a few hours after the ingestion of considerable sodium chlorid, because the salt which enters the blood vessels attracts water from the tissues. The blood concentration is at times increased by eliminating salt from the diet and returns to the normal level when salt is again taken. Curiously enough, water drinking has little effect upon the concentration of the serum in man, nor has moderate sweating from exposure to heat any marked effect. The blood plasma maintains its normal concentration under these circumstances by interchange with the tissue fluids of the body and by variations in the loss of fluid through the kidneys.

Variations Under Pathological Conditions.—In pathological conditions, hydremia is of particular interest in its relation to rapid changes of body weight and to the occurrence of edema. It is well known, for example, that in diabetes a rapid alteration of weight may occur as a result of changes in diet or of the administration of sodium bicarbonate. Such rapid changes are ordinarily due to variations in the water content

of the body. Examinations of the concentration of the blood have generally borne out this view, for with sudden increases in weight the blood often becomes more hydremic and with sudden losses of weight it becomes more concentrated.

In Renal Edema.—In typical renal edema marked degrees of hydremia are usually present. The gain in weight which may follow the administration of sodium chlorid to patients with Bright's disease is associated with a prompt fall in the concentration of the blood serum (Fig.

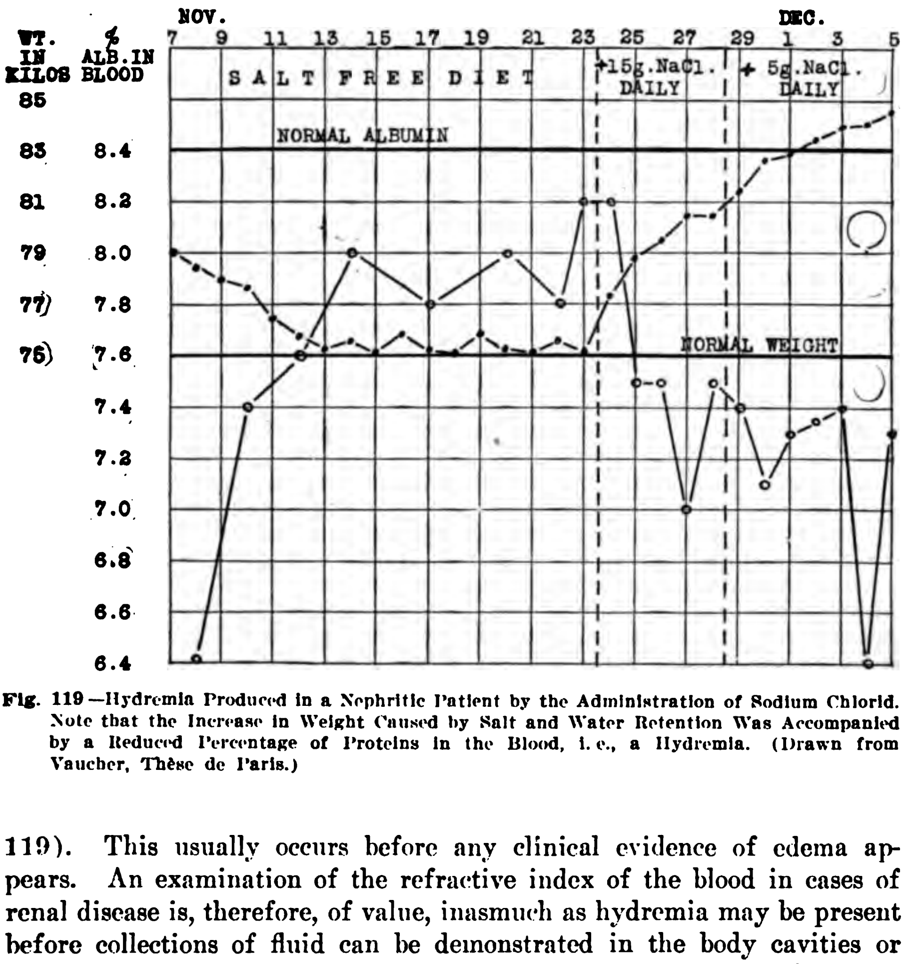

Fig. 119—Hydremia Produced in a Nephritic Patient by the Administration of Sodium Chlorid. Note that the Increase in Weight Caused by Salt and Water Retention Was Accompanied by a Reduced Percentage of Proteins in the Blood, i. e., a Hydremia. (Drawn from Vaucher, Thèse de Paris.)

119). This usually occurs before any clinical evidence of edema appears. An examination of the refractive index of the blood in cases of renal disease is, therefore, of value, inasmuch as hydremia may be present before collections of fluid can be demonstrated in the body cavities or the subcutaneous tissues. So long as this hydremia is present the water metabolism cannot be regarded as normal. In the edema of heart disease, similar relations may or may not be present. As a rule, hydremia is less marked in cardiac than in nephritic edema and cardiac edema may occur with no dilution of the blood serum.

In Infectious Diseases.—Infectious diseases are often accompanied by an hydremic condition of the blood. With the crisis of pneumonia or scarlet fever there may be a rapid fall of weight, a disappearance of hydremia and an unusual elimination of chlorids (Fig. 120). The oc-

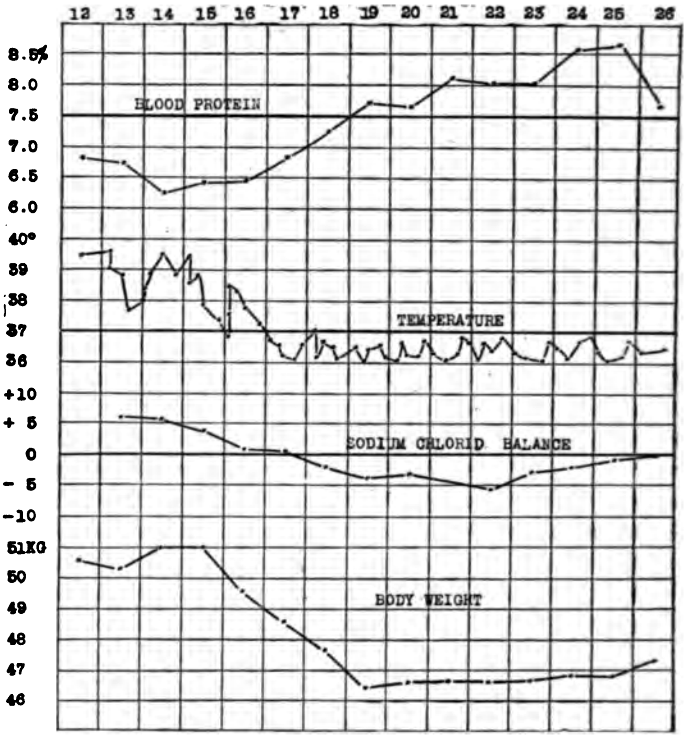

Fig. 120.—Hydremia During Lobar Pneumonia. Note that During the Fever the Percentage of Blood Protein Is Low (Hydremia) and that This Rose When the Fever Fell. (From Sandelowsky, Deutsch. Arch. f. klin. Med., published by F. C. W. Vogel, Leipzig.)

currence of salt and water retention during acute infections has been discussed under Metabolism in Fever.

In Chronic Cachexias.—Finally, in chronic cachexias, especially those due to carcinoma, hydremia is often present. The exact cause of this type is not known.

Hydremic Plethora.—When a rapid, transitory fall in the concentration of the blood occurs, as after the intake of sodium chlorid, the hydremia is obviously due to the addition of water to the blood. Such an increase of blood volume from addition of water is called an hydremic plethora. Hydremic plethora probably also occurs in nephritic edema. In other prolonged types of hydremia, however, we do not know whether the total volume of blood in the body is normal or is increased.

Coagulation, Thrombosis and the Hemorrhagic Diseases

Extravascular Clotting

In spite of the very large amount of work devoted to the study of blood coagulation there still exist wide differences of opinion as to the exact processes involved. For the most part, however, it is now agreed that the final step of coagulation consists of a reaction between the fibrin ferment (thrombin) and fibrinogen, a protein of the blood. When solutions of thrombin are added to solutions of fibrinogen, each being as pure as it can be made, typical coagulation occurs. Coagulation does not occur in the circulating blood, for the reason that no free and active thrombin is present.

Formation of Thrombin.—CALCIUM SALTS.—The formation of thrombin depends upon the interaction of at least three factors. The first of these is the presence of calcium salts. Freshly shed blood may be prevented from coagulating by the addition of oxalates or of other salts which either precipitate or "inactivate" (citrate) the calcium salts. If to such oxalate plasma, calcium salts be added in amounts sufficient to neutralize the oxalate present, coagulation takes place as usual.

SECOND FACTOR: THROMBOGEN, PROTHROMBIN, SEROZYM.—The second factor which is necessary for the formation of thrombin appears to be present in circulating plasma, or to be formed with extraordinary ease in shed blood. Its source is not certain, although it appears to arise in part from the blood platelets. To this factor has been given various names: *thrombogen, prothrombin and serozym.*

THIRD FACTOR: THROMBOKINASE, THROMBOPLASTIN, CYTOZYM.—The third factor is derived from the tissues or from the formed elements of the blood, and particularly from the blood platelets. When oxalated blood is centrifugalized, the major portion of the corpuscles are thrown down. The plasma thus obtained, which is cloudy from the presence of blood platelets, will clot in from eight to fifteen minutes on the addition of recalcifying fluid. If, however, the major portion of the platelets be removed by repeated centrifugalizations, the addition of recalcifying fluid may cause coagulation only after a lapse of forty-five minutes (Lee and Vincent). When platelets are added to such a clear plasma it again coagulates rapidly. Evidently the platelets furnish an element which hastens coagulation. Oxalate plasma which has passed through a Berkefeld filter may fail to coagulate at all when calcium salts are added, but it is possible that in this case other changes than a simple removal of the platelets are responsible for the change.

Extracts from various tissues, while unable in themselves to coagulate pure fibrinogen solutions, furnish an element which hastens the coagulation of blood. The importance of this tissue element is illustrated by the fact

that when the blood of birds and reptiles is taken directly from the blood vessels without coming in contact with the tissues, coagulation is exceedingly slow, and if the cells be removed promptly by centrifugalization, the resulting plasma may not coagulate for days. If, however, such blood comes in contact with the juices of the tissues, or if an extract prepared from the tissues be added to the plasma, coagulation takes place rapidly. To this substance that is derived from the platelets and body tissues various names, such as *thrombokinase, thromboplastin, cytozym,* have been given. According to Howell, thromboplastin is a phósphatid (kephalin) soluble in ether.

Interaction of Formative Substances.—Several views have been expressed concerning the interaction of the substances which take part in the formation of thrombin. According to Morawitz, thrombin is formed directly by a reaction between calcium salts, thrombokinase and thrombogen:

Plasma	Plasma	Cells
↓	↓	↓
Thrombogen	Ca Salts	Thrombokinase
	Thrombin	

Howell believes, however, that the action of tissue juices (thrombokinase, thromboplastin) is best explained by assuming that they neutralize an antithrombin, which is present in the circulating blood where it is united with the prothrombin. When the antithrombin is neutralized prothrombin is set free and it then unites with calcium to form thrombin. His view is indicated by the following reactions:

(prothrombin, antithrombin) + thromboplastin = (thromboplastin, antithrombin) + prothrombin

prothrombin + calcium salts = thrombin

The incoagulable condition of the blood produced by hirudin, a substance that is contained in the extract from leaches, is believed to be due to the antithrombin contained in this extract. According to Howell, the incoagulable blood which follows the intravenous injection of peptone into the dog is also due to an excess of antithrombin in the blood. In such blood, however, there is also a marked reduction in the number of blood platelets.

Thrombosis

The formation of thrombi within the blood vessels of a living animal differs markedly from the extravascular coagulation of blood. The

earliest portion of an intravascular thrombus is white and usually consists of masses of blood platelets which have adhered to one another and to the neighboring vessel wall. The frame work thus produced by the platelets soon becomes surrounded and infiltrated with polynuclear leukocytes. Such a *white thrombus* does not form when a vessel that has been ligated at both ends is removed from the body. It can evidently form only where the blood is in motion. This latter condition is the rule during the earlier stages of thrombus formation within the blood vessels. When once the current of blood has been stopped by a primary thrombus a *secondary red thrombus* develops in the obstructed vessel. This usually extends back to the next anastomosing vessel, and it consists of an irregular mass of red and white corpuscles, blood platelets and fibrin. The secondary red thrombus, therefore, resembles the clot formed during extravascular coagulation. The formation of this secondary thrombus is probably favored by the disintegration of the platelets in the primary thrombus; for, as we have seen, the material derived from disintegrated platelets accelerates extravascular coagulation.

Slowing of Blood Current.—Among the conditions which favor the development of thrombi is a marked slowing of the blood current. This may be due to a general slowing of the blood stream throughout the body (cardiac insufficiency), or it may be due to some local obstruction to the blood flow. Marked slowing also occurs in certain portions of the eddies which always arise when any flowing stream passes an obstruction, a bend, or a sudden widening. It is evident, therefore, that thrombus formation is favored particularly in the irregular dilatations of varicose veins, such as occur in the lower limbs and in the prostatic plexus of elderly men. The bend in the femoral veins near Poupart's ligament, and the dilatation in the blood channel which occurs when the blood enters an aneurism or an auricle, play a rôle in explaining the frequency of thrombi in these locations. Compression of the left iliac vein by the arterial trunks may account for the well-known frequency of thrombosis in the left as compared with the right lower limb.

Changes in Platelets.—It is evident also that changes in the quantity or quality of the blood platelets might influence thrombus formation, but of these changes we know little. After hemorrhage there is a very rapid regeneration of blood platelets and the amount of antithrombin in the blood is diminished. According to K. R. and C. K. Drinker, the latter change is responsible for the more rapid extravascular clotting after hemorrhage. The tendency to intravascular coagulation after operations and confinements may be due in part to both factors.

Injuries or Diseases of Vessel Walls.—Injuries to or disease of the walls of the vessels are also generally regarded as factors favoring the development of local thrombosis. In addition to the eddies produced by an irregular wall, it seems probable that a diseased intima favors an ad-

herence and accumulation of platelets and a liberation of substances that favor clotting (thrombokinase).

Infections and Thrombosis.—Concerning the interrelationship of infections and thrombosis there is still considerable difference of opinion. It is well known that thrombosis occurs not infrequently during the course of infectious diseases, and especially during typhoid fever. Furthermore, thrombi frequently contain microörganisms. In some cases, the thrombi seem to have become infected secondarily, or microörganisms free in the blood stream have been caught mechanically in the thrombus and have undergone further development there. In other cases, the infection seems to be the immediate cause of the thrombus by damaging the vessel wall either through direct extension from the site of infection or possibly through the action of bacteria or toxins that have been carried to some distant point. Whether infection may change the properties of the platelets or other elements in the blood so as to favor thrombosis is not known.

Effect of Injecting Substances into Blood Stream.—The injection of various substances directly into the blood stream may lead to multiple plugging of the blood vessels in different parts of the body. Among the substances which produce intravascular clotting when injected directly into the blood current are various sera either from the same or different species, hemolytic agents, bacteria and foreign bodies in fine suspension, and tissue extracts (thrombokinase). The examination of animals shortly after such an injection shows that the capillaries of certain organs, and particularly of the lungs, the liver, and the spleen, are obstructed by minute thrombi. According to Ashoff, such capillary thrombi may be composed of masses of agglutinated platelets, of the stromata of hemolyzed red corpuscles, of the detritus from injured cells derived from the blood-forming organs, or finally of masses of white corpuscles. Their composition varies according to the cause which produces them. Such occlusions of the capillaries may in certain cases be followed by extensive intravascular coagulation from fibrin formation, and this is particularly apt to happen if the blood platelets are disintegrated. Under such circumstances the coagulability of the blood as whole may be either increased or diminished. When there is a widespread obstruction in the capillaries and the coagulability of the blood is increased, extensive clotting in the heart and larger blood vessels may be found at autopsy. It is an open question, however, whether fibrinous clotting, such as occurs outside of the body, ever occurs as a primary result of such injections. In many cases it certainly follows the plugging of the finer vessels by the agglutinated or disintegrated products of formed elements, that have been derived either from the blood or the blood-forming organs.

Of Substances Influencing Extravascular Clotting.—When substances which are known to influence extravascular clotting are injected into the circulation, the resulting effect upon the coagulability of the

blood is by no means a simple one. We have seen, for example, that tissue extracts contain a thromboplastic substance. When injected in large quantities, they may cause fatal intravascular clotting. When smaller quantities are injected, on the other hand, the blood may clot more slowly than before the injection was made. When pure thrombin is injected even in considerable quantity no demonstrable effect upon the living animal is produced, other than a lengthening of the coagulation time of the blood. The mechanism which causes this slower coagulation of the blood after the intravenous injection of substances which accelerate extravascular clotting is not thoroughly understood. In some cases, capillary thrombi are formed, and these seem to remove certain formed or unformed elements that normally assist clotting. In other cases, it would appear that the injection of thrombin or tissue extracts calls forth a reaction on the part of those tissues which form antithrombin, and that the subsequent fluidity of the blood is due to an excess of this inhibiting substance.

Hemorrhagic Diseases with Reduction in the Blood Platelets

The number of blood platelets to the cubic millimeter of normal blood averages about 450,000, but it may vary from 200,000 to 800,000 without being distinctly pathological. Denys, Hayem and other French observers showed that in certain hemorrhagic diseases there is a striking reduction in the number of blood platelets in the circulating blood, and these findings have been fully confirmed by more recent investigators. Such a reduction of platelets has been found in purpura hemorrhagica, in the hemorrhagic types of certain infectious diseases, especially smallpox and diphtheria, and in certain blood diseases associated with multiple hemorrhages, especially acute leukemia and aplastic anemia. A reduction of blood platelets with hemorrhagic tendency has been produced experimentally by poisoning with large doses of benzol and diphtheria toxin. In these hemorrhagic diseases the number of platelets may fall far below the normal. With moderate hemorrhagic symptoms counts from 40,000 to 100,000 have been obtained while in severe hemorrhagic disease the platelets may be reduced below 10,000 per c.mm. In some cases, it may indeed be difficult to find any platelets in the blood.

Extravascular Coagulation.—In hemorrhagic disease with a reduced platelet count the coagulation of blood which has been removed from the body usually takes place with the usual rapidity. The clot formed often fails to retract in a normal manner. There may be some reduction in the prothrombin but the antithrombin and fibrinogen content of the blood plasma are normal.

Bleeding Time.—Despite the normal coagulation time, Duke has shown that, in these cases, there is a striking change in the duration of the hemorrhage which follows puncture of the ear. In the normal

individual the hemorrhage from such a puncture rapidly lessens. This can be demonstrated by applying blotting paper to the punctured ear at regular intervals (Fig. 121). In patients who show a hemorrhagic tendency associated with a marked reduction in the number of blood platelets, however, the bleeding time from the ear is strikingly prolonged (Fig. 122). Under normal circumstances, the hemorrhage from such a wound seems to be checked mainly by the formation of platelet thrombi in the injured capillaries. When the number of platelets is markedly reduced, these thrombi do not form with normal speed and the bleeding time is, therefore, prolonged.

Fig. 121.—Normal Bleeding Time. (A) From Small Cut; (B) From Larger Cut; and (C) From Very Large Cut. At Half Minute Intervals Absorbent Paper Was Applied to the Cut in the Lobe of the Ear and the Decrease in the Size of the Blood Stains Represents the Rate of Decrease in the Intensity of the Hemorrhage. (From Duke, Arch. Int. Med.)

Cause of Purpuric Eruption.—This increased bleeding time in patients with marked reduction of platelets affords a satisfactory explanation for the long-continued hemorrhages which sometimes follow slight injuries to the mucous membranes. The explanation of the cutaneous and subcutaneous hemorrhages, so characteristic of purpura hemorrhagica and related diseases, is not altogether clear. In some cases, slight injuries or abrasions may have ruptured small blood vessels, and the local hemorrhages have been more profuse than normal by reason of a delay in the formation of platelet thrombi. On the other hand, numerous cutaneous hemorrhages may occur in such patients with no apparent relation to injury. Whether, in such cases, we are to assume numerous insignificant injuries, such as rubbing or scratching, or whether, as seems more likely, there are, in addition, pathological changes in the vessel walls, is still unsettled.

Hemophilia

The classical type of hemophilia occurs in the male members of certain families, being transmitted most commonly through the females. The disease is characterized clinically: (1) by the uncontrollable bleeding which may follow relatively slight injuries, and (2) by the occurrence of joint symptoms after minor injuries, owing to hemorrhages into the joint cavities. All modern students of this disease agree that the blood, when drawn under proper precautions, requires an unusually long time to coagulate outside of the body. Thus Howell found that blood obtained directly from the vein of a hemophiliac did not clot for three or four hours, whereas blood similarly obtained from normal individuals usually clotted in twenty to forty minutes. Addis, using a modification of McGowan's method for estimating the coagulation time, found that whereas normal blood coagulated in nine to eleven minutes, the coagulation time of the blood in hemophilia varied up to ninety minutes or more. He showed, furthermore, from the study of an unusual number of cases, that the severity of the clinical symptoms corresponded to the prolongation of coagulation time, thus proving that the delayed coagulation demonstrable outside the body stands in a direct relationship to the tendency to bleed.

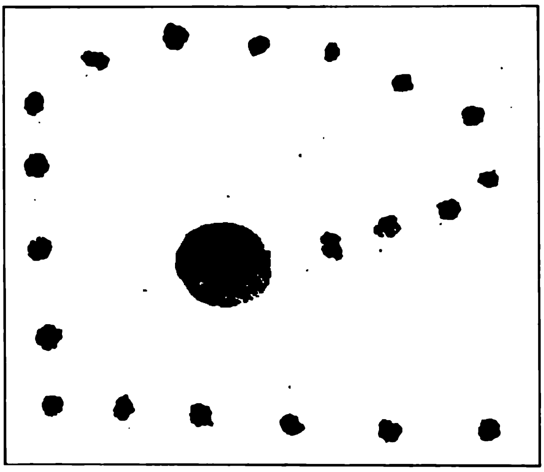

Fig. 122.—Prolonged Bleeding Time. Made from a Very Small Cut in the Ear in the Same Manner As in the Preceding Figure. Note that the Twentieth Stain Was Practically As Large As the First. (From Duke, Arch. Int. Med.)

Cause of Slow Extravascular Coagulation.—The cause of the slow extravascular coagulation of hemophilic blood has been much studied but it is still rather obscure. Examination of the blood shows no marked departure from the normal as regards the red and white corpuscles. The number and appearance of the blood platelets are also normal. No lack of calcium salts in the blood can be demonstrated, and the addition of calcium salts to hemophilic blood does not increase its rate of coagulation to any striking degree. The fibrinogen is normal in amount and it is readily coagulated by thrombin. Howell could find no increase in the antithrombin.

Effect of Added Kephalin.—All modern work has shown that

the coagulation of hemophilic blood is markedly influenced by the addition of tissue extract. In one of Howell's experiments, for example, 1 c.c. of hemophilic blood added to 1 c.c. of a dextrose solution did not begin to clot for over two hours, whereas 1 c.c. of this blood plus 1 c.c. of a dextrose solution containing the active principle of tissue substance (kephalin) coagulated in from ten to eleven minutes. The accelerating effect produced by an admixture of tissue substance is also evident from the fact that in drawing blood from the veins of these patients for test purposes it is important that the puncture be made successfully on the first attempt. Any failure to enter the vein may result in obtaining blood which shows relatively little delay in coagulation. The same is true when blood is obtained by puncture of the skin. Normal blood obtained in this manner usually coagulates more rapidly than blood obtained directly from a vein, but in hemophilia the difference is increased. Indeed, if the tissues about the puncture are squeezed, the blood obtained by such puncture from cases of hemophilia may coagulate in the normal time.

EXPLANATORY HYPOTHESES.—These findings have been variously interpreted. Thus Morawitz and Sahli, on the basis of the coagulation theory of the former, believe that we have in hemophilia a diminution of the element that is derived from the tissues (thrombokinase). This deficiency may arise from qualitative changes in the formed elements of the blood or from changes in the tissues, particularly the vessel walls. Sahli believes that the washed cells of hemophilic blood are less effective in hastening coagulation than the washed cells of normal blood. According to Howell and to Addis, on the other hand, the essential change is in the prothrombin. Howell believes that this is quantitatively deficient and Addis that it is a qualitative defective.

Causes of Prolonged Bleeding.—It is well known that after relatively slight injuries patients suffering from hemophilia may bleed continuously for long periods of time, much longer, in fact, than is required for the coagulation of their own blood even when this is drawn directly from a vein. It may be asked why this prolonged bleeding occurs, and especially so since the blood ordinarily comes in contact with wounded tissue, the juice from which accelerates its extravascular coagulation. Fairly firm clots may form over the wound of a hemophilic patient, but these are apt to be dislodged by slight injuries and when thus dislodged the bleeding begins afresh. Addis has pointed out, that in hemophilia clots form fairly readily over the surface of the wounded tissues. In doing so, however, they prevent the tissue element (thromboplastin) from reaching the blood that flows from the injured vessels. It seems not improbable, in addition, that the continued hemorrhage in hemophilia may be due to some qualitative change in the blood platelets. We have seen that in certain hemorrhagic diseases the platelets are markedly reduced, and that the prolonged bleeding time is due not to a slow coagulation but to a deficient

plugging of the smaller blood vessels by platelet thrombi. In hemophilia it is possible that the slow coagulation and the prolonged bleeding time may both be due to some peculiarity of the platelets which prevents their normal agglutination and disintegration.

Hemorrhagic Disease from Diminished Fibrinogen

Continued hemorrhages may be due to the small amount of fibrinogen in the blood. Such a condition may be produced experimentally in the dog by severe chloroform poisoning. The blood from such animals clots with the usual rapidity, but the clot is flabby on account of the deficient fibrin formed, and it is too weak to make a firm closure of the ruptured blood vessels. Obviously such a condition will favor continued hemorrhage. Fibrinogen originates in the liver and the reduction of fibrinogen in severe chloroform poisoning is to be attributed to the marked hepatic changes which accompany this condition.

In Severe Liver Destruction.—It is well known that a marked tendency to hemorrhage accompanies certain forms of severe liver destruction in man, such as may occur in chloroform poisoning, phosphorus poisoning, acute yellow atrophy of the liver, and yellow fever. It is probable that, in these cases as in the severe chloroform poisoning of dogs, the hemorrhagic tendency is due in part, at least, to a deficiency in the fibrinogen of the blood. Whipple and his coworkers have shown that in chronic cirrhosis of the liver the fibrinogen is frequently less than normal, and at times it is so low that it may be regarded as the cause of the hemorrhagic tendency.

Other Hemorrhagic Conditions

In most other conditions showing a tendency to hemorrhage, there is neither a reduction in the number of platelets nor a reduction in the amount of fibrinogen. It is possible that, in some cases, there may be a qualitative change in the blood platelets, but of this we have no definite information. In most studies of such bloods it has been assumed that the hemorrhages were due to delayed coagulation, and efforts have been made to determine which of the various factors that control normal coagulation was altered and was thus responsible for the slow coagulation.

Diminished Calcium.—Only rarely can delayed coagulation be attributed to a deficiency or inactivity of the calcium salts. Possibly this is the cause of the slow coagulation in certain cases of obstructive jaundice, for the addition of calcium salts to the blood or the administration of calcium salts to such patients frequently seems to shorten the coagulation time (Lee and Vincent).

Excess of Antithrombia.—Among other factors which have been held responsible for delayed coagulation may be mentioned: (1) a de-

ficiency in the prothrombin; (2) a deficiency in the thromboplastin; and (3) an excess of antithrombin. The latter, as we have seen, is the cause of the incoagulability of hirudin blood and probably also of peptone blood. According to Whipple, it is also responsible for a large number and great variety of clinical forms of delayed coagulation, such as occur in septicemia, pneumonia, endocarditis, miliary tuberculosis, general vascular thrombosis, etc.

Deficient Prothrombin.—According to the same author, a deficiency of prothrombin in many, and perhaps in all instances, characterizes the condition of melena neonatorum. Certainly the striking benefit derived by the latter group of patients from injections of serum or from the direct transfusion of blood indicates that the disease arises from some deficiency in one of the clotting factors. Morawitz is inclined to lay great stress upon an absence of thromboplastic substances as an etiological factor in obscure hemorrhagic diseases. It must be admitted, however, that, at the present time, the study of these hemorrhagic conditions is hampered by the fact that much is uncertain concerning the physiology of blood coagulation and the spontaneous cessation of hemorrhage from open vessels. Furthermore, it must be borne in mind, that in the purpuras with diminished platelet counts we have hemorrhagic conditions not associated with any definite reduction in the extravascular coagulation time. It is possible that qualitative changes in the blood platelets, of which we know nothing at the present time, are responsible for certain failures to arrest hemorrhages.

Pathology of the Red Blood Corpuscles

Increased Destruction Hemolysis

The Rate of Destruction

There is a constant disintegration and regeneration of the red corpuscles in the body. We do not know the exact rapidity with which this takes place. Estimates are based mainly upon the daily excretion of bile pigments, or of urobilin and related substances, which are derived from the hemoglobin of the red cells. By this method it has been estimated that under normal conditions from one-tenth to one-twentieth of all the red cells in the body are destroyed daily. The average life of the erythrocyte would, therefore, be from ten to twenty days. Under pathological conditions the rate of destruction may be very markedly increased. During acute attacks of hemolysis, such as occur in blackwater fever, this is plainly evident from the rapid fall of hemoglobin during the attack. An increased destruction may also occur as a chronic condition. In chronic hemolytic jaundice, for example, the amount of urobilin excreted in the

stools and urine is so large that the average life of the red corpuscle can hardly be more than two or three days (Eppinger and Charnas).

Types of Destruction

Just where and how this destruction takes place is not known. As Hunter has pointed out, two separate processes may be distinguished. The first of these is hemolysis in the narrower sense, a solution of the red cells in the circulating blood. This almost certainly occurs in those pathological conditions where considerable quantities of free hemoglobin can be demonstrated in the blood plasma and where hemoglobin passes into the urine. Under normal conditions, however, it is probable that red cells are rarely if ever dissolved directly in the plasma. Free hemoglobin is almost never found in the normal circulating blood, and it may be absent even when we know that there is an increased rate of blood destruction.

Activity of Erythrophages.—The second method for disposing of the erythrocytes is through the phagocytic activity of certain cells. It is known that large endothelial cells in the spleen frequently contain erythrocytes and detritus from disintegrating erythrocytes; and it seems probable that similar cells in other parts of the body, and especially in the liver, the lymph glands and the bone marrow, may perform a like function. These erythrophages certainly remove badly damaged or decrepit red cells from the circulating blood, for they contain an increased amount of detritus after the action of substances which injure the red cells. Whether, in addition, these cells may play an active part in blood destruction by attacking and destroying relatively healthy cells is not known.

Manifestations of Increased Hemolysis

The manifestations of a very rapid destruction of red cells in the body are caused in part by the liberation and disintegration of hemoglobin and in part by the toxic or mechanical action of the erythrocytic stromata.

Hemoglobinuria.—If the concentration of hemoglobin in the plasma exceeds a certain limit, it is excreted by the kidneys, giving rise to hemoglobinuria. The concentration which must be reached before hemoglobinuria occurs has been placed by Pearce and his coworkers at approximately 0.06 gram of hemoglobin per kilo of body weight for the dog, a figure which is somewhat less than the older estimate of 1/60 of the total hemoglobin. It seems probable, however, that under pathological conditions the renal threshold for the excretion of hemoglobin may be lowered. In a case of paroxysmal hemoglobinuria, recently reported by Dennie and Robertson, for example, it was found that hemoglobinuria occurred even though only small amounts of blood were hemolysed.

In hemoglobinuria the urine usually contains albumin and casts and

the kidneys show a severe degeneration of the renal parenchyma with desquamation of the renal cells. When the destruction of red cells is very marked anuria may result.

Jaundice.—Whenever there is an increased destruction of red corpuscles, the increased amount of hemoglobin set free causes an increased formation of bile pigments. The latter may be almost wholly excreted by the liver, or bile pigments may be retained in the body to such an extent that jaundice is produced. Apparently no very exact relationship exists between the rate of blood destruction and the degree of jaundice present. Changes in the liver cells, in the bile capillaries or in the viscosity of the bile probably play rôles in determining the incidence and severity of the jaundice (see Jaundice). Variations in the renal permeability to hemoglobin would also influence the level of hemoglobin in the blood and the amount available for bile pigment formation.

Fever and Toxic Symptoms in Acute Hemolysis.—Acute attacks of hemolysis from whatever cause are often associated with fever and with toxic symptoms. Apparently these symptoms depend only to a minor degree upon the liberation of free hemoglobin. These toxic effects are more commonly produced by the stromata of the disintegrating erythrocytes; for the injection of pure hemoglobin solutions into animals is less poisonous than the injection of the erythrocytic stromata after the removal of hemoglobin. In all conditions of rapid hemolysis the spleen becomes enlarged. This is due, in part at least, to an accumulation therein of the disintegrated red cells and their stromata (spodogenous enlargement).

Urobilin Excretion.—The destruction of erythrocytes in the body may be increased to a moderate or considerable extent without producing either hemoglobinuria or jaundice. The increased amount of bile pigments derived from the liberated hemoglobin is removed almost entirely by the liver and is excreted in the bile. Unfortunately, it is not possible to determine directly the amount of bile pigments that are formed in the bodies of such patients. Approximate estimates of these amounts can, however, be made. In the intestines the bile pigments are converted into urobilinogen and urobilin. These pigments are partially resorbed from the intestines and some may then pass through the liver and be excreted in the urine. A considerable part, however, is excreted in the stools and the total amount of these pigments in the stools and in the urine is a rough measure of the rate of erythrocytic disintegration.

Deposition of Insoluble Pigments.—Increased hemolysis may also lead to the deposition of insoluble pigments in various organs. Some of these give the chemical reactions of iron (hemosiderin), others fail to do so. These pigments are deposited particularly in the liver, the spleen, the kidney and the bone marrow.

Causes of Hemolysis

In many respects the red blood corpuscles behave as if they were surrounded by semipermeable membranes which allow certain substances to pass through more freely than others. The retention of hemoglobin within the cell is often ascribed to such a membrane. That this is not the correct explanation for this retention is evident, however, from the fact that even when red cells are cut into pieces in isotonic salt solution the hemoglobin does not escape. It seems intimately bound by chemical or physical means to the stromata of the red cells. When hemoglobin is discharged from the red cells, the fluid loses its opaque red color and becomes more transparent. This process is called hemolysis.

Many substances will cause an escape of hemoglobin from the erythrocytes and the mechanism of hemolysis varies according to its cause. Furthermore, the substances which cause hemolysis in the test tube are not always equally effective in the body, for the latter can protect itself to some extent against certain hemolytic agents. Conversely, certain substances which have little or no hemolytic action in the test tube are active destroyers of red cells when introduced into the body.

1. *Hemolysis by Hypotonic Salt Solutions*

With respect to sodium chlorid and a number of other salt solutions the red corpuscle behaves as if it were surrounded by a semipermeable membrane which permits the free passage of water but restricts the passage of salts. Indeed, the salts normally present in red corpuscles differ from the salts present in plasma, being poor in sodium chlorid and rich in potassium salts. When erythrocytes are placed in an isotonic sodium chlorid solution (0.9 per cent), no change occurs in their appearance. When the salt solution is more concentrated (hypertonic), water leaves the corpuscles, they shrivel up, and they may eventually discharge their hemoglobin. When the salt solution is less concentrated (hypotonic), the corpuscles take up water, swell, and finally discharge their hemoglobin. With normal corpuscles, hemolysis begins in solutions containing about 0.42 per cent of sodium chlorid, and hemolysis of all the cells occurs in solutions containing about 0.36 per cent of sodium chlorid. The ease with which the corpuscles give up their hemoglobin when exposed to diminishing concentrations of salt solution is called the corpuscular fragility. In certain diseases, and particularly in cases of congenital hemolytic jaundice, some or all of the corpuscles do not withstand dilute salt solutions to a normal degree. Their fragility is said to be increased.

Other salts, especially the ammonia salts, have a specific hemolytic effect upon the red cells. They cause hemolysis even when the solution contains the same number of molecules as an isotonic sodium chlorid solution.

2. Lipoids and Lipoidal Solvents

The stromata of the red corpuscles contain a certain amount of lipoidal material which is soluble in alcohol and ether. Various substances cause hemolysis because they possess an affinity for this portion of the red cells. Among these are ether, chloroform, bile salts, soaps, and amyl alcohol. These substances are in general more destructive to corpuscles suspended in salt solution than to corpuscles suspended in blood serum or plasma, probably because the proteins and lipoids contained in these latter fluids take up the destructive agent.

Saponin Hemolysis.—The saponins, which are powerful hemolytic agents, act in a manner similar to the lipoidal solvents, for they combine with cholesterin and with lecithin. In the test tube their action on red cells may be prevented by the addition of cholesterin. Studies on patients have emphasized the fact that the resistance of red cells to saponin hemolysis differs from their resistance to hemolysis by hypotonic salt solution, for the two do not vary in the same directions in different pathological conditions. In obstructive jaundice and in pernicious anemia, for example, the resistance of the erythrocytes to hypotonic salt solution is increased whereas their resistance to saponin is diminished.

3. Snake Venoms

The venoms from the poisonous snakes (cobra, water moccasin, copperhead and rattlesnake) all contain hemolytic substances. The hemolytic substance of cobra venom is only destructive to washed red corpuscles in the presence of lecithin. Like many other hemolytic substances, these snake venoms also cause agglutination of the red blood cells, but the agglutinative properties do not appear to run parallel to the hemolytic properties. The resistance to hemolysis by cobra venom is usually increased in the later stages of syphilis, a fact which has been used for diagnostic purposes.

4. Bacterial Hemolysins

Hemolytic substances have been extracted from various bacteria, and these are doubtlessly responsible for the definite signs of hemolysis which occasionally occur during the course of infectious diseases. Whether the anemia which develops during so many infections is due mainly to these hemolytic substances or to other factors is not definitely determined.

5. Hemolysis by Specific Immune Sera

It has long been known that the sera of certain animals will dissolve the red corpuscles of animals belonging to certain other species. Where

the serum does not possess this property originally, it may be developed if the animal receives repeated injections of the foreign corpuscles. By this means an active hemolytic serum is produced, which acts only against the type of corpuscles that has been injected. Such specific hemolytic sera have proved of great interest in immunity studies, for the reason that the mechanism of their formation and action is similar to that which enables the blood serum to destroy bacteria or other foreign cells (see Bactericidal Properties of Blood Serum).

Amboceptor and Complement.—Through the classical work of Bordet, Ehrlich and their collaborators it has been shown that when a hemolytic serum has been produced by the injection of foreign corpuscles, its activity is due to the presence of two substances. The first of these, the so-called amboceptor or immune body, is of a specific character and acts only against the type of cells that has been injected. The unusual activity of immune sera is due to the increased amounts of amboceptor which they contain. The second body, or complement, is probably non-specific and it is not increased during the process of immunization. Since the immune body withstands a higher temperature than the complement, it is possible to destroy the latter by heating the serum to 55° C. for one hour. Such an inactivated immune serum does not destroy the red corpuscles against which it has been prepared; but if the complement be added the mixture produces rapid hemolysis. There is a strong affinity between the red blood corpuscles and their amboceptors. If erythrocytes be allowed to remain in an inactivated immune serum and then be separated by centrifugalization, they carry out the immune body with them. Such corpuscles may then be hemolyzed by placing them in a fresh non-immune serum.

Hemolytic immune sera destroy the red corpuscles through their action on the stromata of the red cells and such sera can be produced by the injection of washed stromata from erythrocytes after removal of the hemoglobin.

6. *Hemolysis by Non-immune Sera*

In addition to the hemolytic activity which develops as a result of the injection of foreign erythrocytes, the blood sera of certain animals possess natural hemolytic properties toward the corpuscles of certain other animals. In such cases, also, the hemolysis is due to the combined action of amboceptor and complement.

Isohemolysins; Autohemolysins.—As a rule, the sera derived from animals of a given species do not hemolyze the corpuscles of other animals belonging to the same species. Occasionally, however, this occurs and such sera are said to possess isohemolysins. When, as rarely happens, the serum of a given animal will dissolve its own corpuscles, the serum is said to possess autohemolysins. The possible presence of isohemolysins is of great importance when direct transfusions of blood are made from one

individual to another, and they will be considered later (see Transfusion of Blood).

Association of Isohemolysins with Certain Diseases.—Efforts have been made to show that isohemolysins appear in the blood of patients suffering from certain diseases. Crile believes, for example, that the sera of cancer patients possess unusual hemolytic properties. While this seems to be true in a general sense, it is not a constant phenomenon, and it is not restricted to the sera derived from cancer patients. Its value as a diagnostic aid is, therefore, not established.

Paroxysmal Hemoglobinuria

Paroxysmal hemoglobinuria is characterized by remarkable attacks of acute hemolysis within the blood vessels. The exciting cause of such attacks is usually exposure to cold, and attacks may be produced artificially by immersing the hands of susceptible individuals in cold water. If the veins leading from the cooled extremity be obstructed hemolysis occurs locally, but not in the remainder of the body.

Symptoms.—The paroxysms themselves are characterized by the typical manifestations of severe acute hemolysis: hemoglobinemia, hemoglobinuria, fever, enlargements of the liver and spleen, and occasionally jaundice. The frequent absence of jaundice may be due to the unusually rapid excretion of hemoglobin by the kidney, such as occurred in the case reported by Dennie and Robertson.

Mechanism of Hemolysis.—The mechanism of hemolysis in these patients has been studied particularly by Eason and by Donath and Landsteiner. These investigators showed that the solution of erythrocytes was caused by a peculiar autohemolysin. When the patient's serum, freshly prepared, is mixed either with his own or with another person's red corpuscles and the mixture is cooled, the hemolytic substances combine with the red blood corpuscles and on subsequent warming, hemolysis occurs. The degree of cooling that is necessary in order to effect this combination between erythrocytes and hemolysins varies in different individuals. In some an ordinary room temperature of 15° to 22° C. suffices, while in others the mixture of serum and erythrocytes must be cooled in an icechest. These differences correspond to the observed difference in the ease with which paroxysms may be induced in various patients. It seems probable, however, that the hemolysis occurs more readily within the body of the patient than it does in the test tube. There is no evidence that the red blood corpuscles of these patients are altered in such a manner as to render them unusually liable to hemolysis.

Associated Vascular Spasm.—We have said that attacks of hemoglobinuria are usually induced in susceptible patients by exposure to cold. A contributory factor, which is frequently present, is the tendency toward vascular spasms in the peripheral parts of the body. As a result of such

vascular spasms the circulation in an affected extremity becomes exceedingly slow, and this allows the temperature of the contained blood to approach that of the surrounding air.

Relation to Syphilis.—The underlying cause of paroxysmal hemoglobinuria is usually a syphilitic infection. Many patients give a history or show stigmata of old syphilis, and a positive Wassermann reaction has been found in as high a proportion as 90 per cent of the patients examined. Recoveries under antisyphilitic treatment have also been reported.

Blackwater Fever

Blackwater fever, a condition which occurs almost exclusively among inhabitants of the tropics, is characterized by severe paroxysms of hemolysis within the blood vessels. The principal symptoms and signs—fever, hemoglobinuria, jaundice, anemia, urinary changes and splenic enlargement—may all be attributed to the rapid destruction of red corpuscles. It is noteworthy, however, that the accompanying jaundice is distinctly more marked than in paroxysmal hemoglobinuria.

Relation to Malaria.—It has long been known that blackwater fever occurs chiefly, and perhaps exclusively, in those who have been infected with malaria. Its exact relationship to malaria is not altogether clear, however, for the attacks are frequently precipitated by the administration of quinin, a drug which destroys the malarial parasites.

Number of Parasites in Peripheral Blood.—In malaria the rate of erythrocytic destruction is increased. The infected red cells disintegrate during sporulation of the parasites, pigments probably derived from hemoglobin are deposited in various parts of the body and the excretion of urobilin in the stools is increased. In severe malarial infections, therefore, one would expect to find a more rapid disintegration of red cells. It is a noteworthy fact, however, that in blackwater fever the number of malarial parasites found in the peripheral blood bears no definite relationship to the severity of the attacks. It has been indeed a common observation that the number of parasites in the peripheral blood diminishes markedly during or just after the attack, and many cases have been reported in which no blood parasites could be found. Probably, however, the parasites are always present in the internal organs.

Attacks Frequently Precipitated by Quinin.—The immediate cause of the destruction of red cells which leads to blackwater fever is not known. Brem describes a hemolytic substance in malarial parasites and it may be that this is responsible for the attack of hemolysis. Of particular interest, however, is the fact that the attacks are frequently precipitated by the administration of quinin. Various substances chemically related to quinin are known to possess more or less marked hemolytic properties; and the administration of quinin to normal individuals

is said to increase the excretion of urobilin in the stools (Barratt and Yorke). It is quite possible that in certain malarial infections there are changes in the red cells which render them peculiarly liable to this action of quinin. Concerning this, however, we have no positive evidence.

Hemoglobinuria from Other Causes

Hemoglobinuria has been observed occasionally in man from a variety of other causes. Among these are extensive burns as well as the action of various poisons, such as arseniureted hydrogen, carbolic acid and snake venom. It is noteworthy that arseniureted hydrogen, which produces hemoglobinemia in the body, does not hemolyze red corpuscles in a test tube. Hemoglobinuria also occasionally accompanies severe infections, particularly sepsis and scarlet fever. It may also follow the transfusion of blood.

Methemoglobin and Red Cell Destruction

Methemoglobin differs physiologically from oxyhemoglobin in that the oxygen is firmly bound to the hemoglobin and is not readily dissociated. For respiratory purposes, therefore, methemoglobin is useless. Its presence in the blood gives to the latter a dark chocolate color and patients with methemoglobinemia usually present the appearance of cyanosis. It is probable that during intense hemolysis from any cause some methemoglobin is formed. In certain types of poisoning, however, the methemoglobin formation antedates the destruction of the red blood corpuscles, and the latter may not be sufficiently rapid to cause evident signs and symptoms. In other cases, it causes anemia, jaundice, methemoglobinuria and disturbances of kidney function.

Drugs Leading to Its Formation.—Among the drugs which may lead to the formation of methemoglobin are potassium chlorate, the nitrites and various anilin derivatives, particularly acetanilid. Years ago Marchand pointed out the danger of administering considerable quantities of potassium chlorate, as was then the custom in the treatment of diphtheria. More recently, emphasis has been laid upon the danger of methemoglobin formation from the excessive use of the anilin derivatives commonly present in headache remedies. Methemoglobin is also found in severe pneumococcus infections.

Increased Destruction of Erythrocytes Without Evident Signs

The types of red cell destruction thus far considered have been of such a character as to produce striking clinical symptoms or signs. It is evident, however, that a less marked or more gradual destruction may produce neither hemoglobinuria nor jaundice, although if long continued

it might constitute a serious drain upon the blood. Evidence of such an increased destruction is furnished by the demonstration of an increased excretion of urobilin and of urobilinogen and by a deposition in the various organs of pigments derived from hemoglobin. We know, for example, that in certain forms of anemia, particularly pernicious anemia, such evidence is present. We are still very ignorant concerning the nature of the destructive process in most of these cases. The red cells may be destroyed through hemolytic agents of an unknown nature, or possibly through an increased phagocytic activity of certain cells in the body. In experimental trypanosome anemia, for example, there is a marked phagocytosis of erythrocytes by the endothelial cells of the lymphatic glands, the liver and the spleen. The same occurs in animals that have received injections of hemolytic sera. Such an increased cellular activity may simply remove from the circulation those red cells that have been previously damaged, and in this way it may prevent the evil consequences of a direct solution of erythrocytes in the blood stream. On the other hand, the phagocytic cells may possibly contribute to the blood destruction by taking up cells that are still healthy.

Regeneration of Red Corpuscles

Under normal conditions the total number of red cells in the body varies but slightly. There is a delicate physiological adjustment between destruction and new formation. Any loss or destruction of erythrocytes calls forth any increased new formation with a consequent tendency to return to the normal cell count.

Clinical Evidence of Increased Regeneration

Unfortunately, we have no satisfactory clinical method for determining directly the rate at which new red cells are formed in the living subject. So long as the blood remains constant, however, the rate of regeneration must be equal to the rate of destruction. Indirectly, therefore, the rate of regeneration may be roughly estimated by determining the amount of urobilin and of urobilinogen excreted in the stools and urine.

Immature Nucleated Forms in Peripheral Blood.—Qualitative evidence of an increased formation of red cells may often be obtained on microscopic examination of the blood. During periods of rapid regeneration a certain number of immature, nucleated forms often escape from the bone marrow into the circulation, so that the presence of nucleated erythrocytes in the peripheral blood indicates an increased activity of the blood-forming tissues. The number of nucleated red cells is, however, no quantitative measure of the rate of new cell formation, for immature cells may be thrown into the circulation by qualitative as well as by quantitative changes in the regeneration. When, for example, malignant tumors in-

vade the bone marrow, nucleated red cells may appear in the peripheral circulation in great numbers; yet this seems to be due to a direct damage to the marrow rather than to a high rate of new cell formation.

Staining Peculiarities.—The presence of basic staining granules in fixed blood preparations and of reticulated (granulofilamentous) corpuscles in preparations that have been stained by vital methods, appears to indicate an immaturity of the cells. Such staining peculiarities may possibly occur in old cells, but it seems probable that this is rarely if ever the case in the blood stream of man.

According to Morawitz, immature red cells use up oxygen with unusual rapidity when they are incubated under anaërobic conditions. He believes that this property may give positive evidence of new formation when the microscopic evidence is negative. According to Masing, immature blood may be further distinguished from that which is more mature by the fact that it contains a larger amount of nuclein phosphorus.

Anatomical Evidence of Increased Regeneration

At autopsy an excessive new formation of red cells may be suspected when the red marrow of the bones has extended beyond its usual confines. The activity of the bone marrow may also be estimated by its richness in nucleated red cells. Finally, when the regeneration of erythrocytes has been rapid, areas of new formation may be found outside of the bone marrow and particularly in the spleen and in the liver.

The Stimulus to Regeneration

The mechanism which regulates the new formation of red cells is evidently delicately adjusted to the needs of the body, for the number of erythrocytes remains remarkably constant under varying conditions. As yet, however, we know little concerning this mechanism.

Stimulation by Diminished Oxygen Supply.—It has been suggested that a diminished oxygen supply to the bone marrow may stimulate the new formation of erythrocytes, and it is an interesting fact that in a variety of conditions which evidently lessen the oxygen supply to the body, such as the anemias, cyanosis, diminished atmospheric pressure and carbon monoxid poisoning, there appears to be an increased formation of erythrocytes. It is not certain, however, that this is the normal mechanism which governs the new formation of red cells.

Stimulation by Products of Hemolysis.—In experimental anemias the regeneration of red cells varies according to the cause. In anemias produced by hemolytic agents the evidences of regeneration are more numerous than in anemias produced by hemorrhage. Unripe cells occur in the peripheral blood in greater numbers, areas of red cell formation outside of the bone marrow are more common, the restoration of the normal blood

count is more rapid and the red cells show a greater oxygen consumption (Morawitz). These differences may be due either to a loss during hemorrhage of certain substances that are necessary for the reconstruction of red cells (iron), or they may be due to the stimulating effect of substances derived from the erythrocytes during their hemolysis. Kepinow found that the injection of lipoids derived from red cells accelerated recovery from experimental anemia, and Morawitz believes that the favorable effects which sometimes follow an injection of blood into anemic individuals are due, not so much to the red corpuscles that are introduced, as to their stimulating effect upon the blood-forming organs. The occurrence of remissions in pernicious anemia after blood transfusion may be best explained in this manner. Morawitz suggests, furthermore, that the products of erythrocytic disintegration may furnish a normal stimulus to regeneration, and that it may thus serve to maintain a constant composition of the blood in the body.

Types of Regeneration

Simple.—Two general types of blood regeneration are commonly distinguished. The first and more common type is characterized by the presence of red corpuscles that are poor in hemoglobin (low color index). Their size and shape are approximately normal and changes in their staining properties, though often present, are rarely extreme. Relatively few nucleated red cells escape into the general circulation and these are usually of the normoblast variety. This is called the *simple or normoblastic type of regeneration.* In man it is the common form after hemorrhages and most other well recognized causes of anemia.

Pernicious.—The second type of regeneration is typefied by that seen in pernicious anemia. It is characterized by a reduction in the number of red corpuscles which equals or exceeds the reduction in the amount of hemoglobin (high color index). This high color index is due to a high content of the individual cells in normal hemoglobin and is not due to any change in the composition of this pigment (Butterfield). In this type of regeneration basic staining granules in the cells are common and unusually large red cells either nucleated (megaloblasts) or non-nucleated (megalocytes) are present. It is therefore called *the pernicious or megaloblastic type of regeneration.* The variations in shape of the red cells and the unusually small forms, both of which are common in this type of anemia, are believed to be due to degenerative rather than to regenerative changes.

Although these two types can usually be separated, transitions do occur, and in the toxic anemias that have been produced experimentally in animals it has often proved difficult to classify the anemia. Furthermore, the normoblastic regeneration, which is the rule after hemorrhage, may

in animals be replaced by a megaloblastic picture if the hemorrhages are frequently repeated.

Cause of Difference.—The cause of the difference between these two types of regeneration is not certain. That the megaloblastic type is due exclusively to an unusually rapid or an unusually prolonged regeneration of new cells is rendered improbable by the fact that in chronic hemolytic jaundice remarkable increases in the excretion of urobilin occur without a megaloblastic blood picture; whereas in pernicious anemia the excretion of urobilin, though increased, is usually less marked than in chronic hemolytic jaundice. Apparently the megaloblastic type of regeneration depends upon quantitative changes in the bone marrow, which may be brought about either by exhaustion or by the direct action of toxic substances.

Anemia

General Considerations

The term anemia, though meaning a lack of blood, has come to be applied more specifically to those conditions in which the number of red cells or the amount of hemoglobin to the unit of blood volume is diminished.

Skin Pallor.—Skin pallor is not necessarily due to anemia. The normal tint of the skin is determined in part by its pigments and in part by the quantity and quality of the blood that it contains. The pallor of fainting, for example, is obviously due to a lack of blood in the cutaneous vessels. Certain persons habitually have a pale skin even though the blood shows no deficit in hemoglobin. In such cases the pallor is presumably due to a chronic narrowing of the skin capillaries and venules, or possibly to an unusually thick and but slightly pigmented skin. Such pallor may occur when the individual appears to be in perfect health or again it occurs in association with certain pathological conditions. Persons who live under poor hygienic conditions often appear pale even though the blood shows no anemia. The combination of hard work, poor food and dark or poorly lighted work rooms or dwellings produces such a pallor which may or may not be associated with demonstrable anemia. It is a common experience also that patients with nephritis appear pale, even when the hemoglobin content of the blood is approximately normal. Possibly in such cases the pallor is due to an increased amount of fluid in the cutaneous tissues.

Relation to Total Blood Volume.—The ordinary picture of anemic blood may be due not to a reduction in the total amount of hemoglobin in the body, but to the presence of an excessive amount of plasma. In order to estimate the total number of red cells or the total quantity of hemoglobin in the body, it is necessary to know the total blood

volume. In the following discussion of anemia, reference will frequently be made to the total blood volume, as determined particularly by the carbon monoxid method. It should be remembered, however, that the accuracy of methods for determining the total blood in the body is still somewhat open to question, so that at present this factor constitutes an uncertain element in blood studies.

Variation in Number of Red Cells.—If variations in blood volume be omitted from consideration, then any fall in the red cell count indicates that more red cells are being destroyed than are being formed, and any rise in this count indicates a difference in the opposite direction. When the number of cells in the blood remains constant the number formed must equal the number destroyed. During stationary periods of anemia or health, therefore, a more or less exact balance exists between blood destruction and blood regeneration.

Determination of Number.—During such stationary periods the number of cells in the blood is determined: (1) by the average life of the individual cells; and (2) by the rate at which new cells are formed (and old ones destroyed). It is obvious, for example, that if the average life of the individual corpuscles be lessened while the rate of new formation (and disintegration) remains constant, there will be fewer erythrocytes in the blood (*Anemia from Blood Destruction*). Also, if the rate of new formation (and destruction) be lessened with no change in the average life of the cells, the number of erythrocytes in the blood will be low (*Anemia from Lessened New Formation*). Anemia may, therefore, be due to either of these causes or to their combination. On the other hand, a normal blood count may be present, not alone when the conditions governing blood formation and blood destruction are in every way normal, but also when a shortened life of the average corpuscle is accompanied by an increased rate of new formation (compensation of increased destruction by increased new formation).

The classification of anemias is based upon these principles; and although it is difficult to fit certain clinical forms into any rational scheme, the following may be used as a working classification:

Classification of Anemias

I. Anemia from Increased Losses of Red Cells.

   1. Anemia from hemorrhage.
   2. Anemia from blood destruction (toxic, etc.).

      a. With simple (normoblastic) regeneration.
      b. With pernicious (megaloblastic) regeneration.

II. Anemias from Lessened Formation of Cells or Hemoglobin.

III. Anemias due to an Increase in the Blood Plasma.

Anemia from Hemorrhage

During and after an acute hemorrhage, liquids pass from the tissues into the blood vessels. This dilution of the blood occurs so rapidly that blood coming from an open artery becomes perceptibly lighter in color at the end of fifteen minutes of moderate bleeding. In man also a dilution of the blood has been demonstrated within half an hour after bleeding. Indeed the volume of blood in the vessels shortly after a hemorrhage of 300 c.c. may be greater than it was before. Thus Reiss found that after such a hemorrhage the concentration of blood protein, as determined by the refractometer, fell from 7.2 per cent to 6.1 per cent, whereas the calculated percentage in case the blood lost had been replaced by protein-free salt solution was 6.7 per cent. Similarly Boycott and Douglas determined the quantity of blood in the body of rabbits by the carbon monoxid method and found that after hemorrhage there might be an increased amount of blood, owing to an excessive inflow of fluid from the tissues. The fluid that is first added to the blood is relatively poor in proteins, but within a few hours or days the composition of the plasma becomes normal.

The rapidity with which fluid is replaced in the blood vessels after a hemorrhage depends upon a variety of factors. Among these are the severity of the hemorrhage, the amount of available liquid in the body and the type of animal. Rabbits, for example, seem to replace the lost fluids more rapidly than dogs. Owing to the continued addition of fluid to the blood the percentage of hemoglobin may continue to fall for some days after the hemorrhage has ceased.

Replacement of Lost Fluid.—The amount of blood that may be lost without producing a fatal result varies. When the hemorrhage takes place very rapidly a loss of 50 per cent of the total blood may be fatal; whereas when the hemorrhage takes place gradually, larger losses may be recovered from. Since the immediate effect of an acute hemorrhage is due in large part to the reduction of blood volume, it is important from the therapeutic standpoint that sufficient liquid be placed at the disposal of the body to maintain the blood volume. Clinical as well as experimental evidence indicates that salt solution is rapidly absorbed from the rectum and lower bowel. Except in great emergency, therefore, the rectal administration of salt solution provides the necessary liquid for the maintenance of blood volume.

The dilution of the blood which follows an acute hemorrhage causes a reduction in the number of red cells and in the amount of hemoglobin to the unit of blood volume. It is evident, however, that this reduction can be used as a measure of the blood lost only in case the blood volume returns to and remains at the original level. It is by no means certain that this always occurs. In Figure 123, for example, it will be seen that although the percentage of hemoglobin remained low for a long time after

the hemorrhage, an increase in blood volume tended to compensate for this deficit and the total hemoglobin in the body approached and later exceeded the normal. Although such changes of blood volume may not be

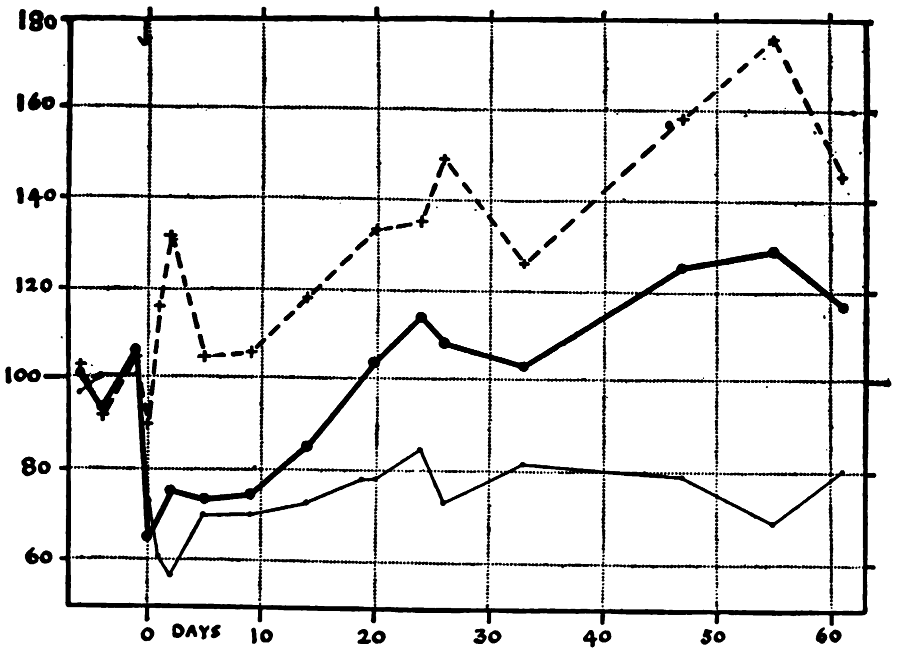

Fig. 123.—Effect of a Single Hemorrhage upon the Hemoglobin and Blood Volume of a Rabbit. The Thin Line Represents the Percentage of Hemoglobin in the Blood, the Broken Line Represents the Blood Volume, and the Heavy Line the Total Amount of Hemoglobin in the Body. Note that the Immediate Effect of the Hemorrhage Was a Reduction in the Percentage of Hemoglobin and that This Percentage Continued to Fall for Two or Three Days. The Percentage Rose After This But Did Not Reach the Original Percentage. The Increase in the Blood Volume, However, During the Later Portions of the Curve Caused an Increase in the Total Amount of Hemoglobin in the Body. (From Boycott and Douglas, Jour. Path. and Bacter.)

the rule, they illustrate the point that data derived from color readings alone may not give a proper conception of the total hemoglobin in the body after hemorrhage.

Increased Production of Red Cells.—The loss of blood after acute hemorrhage leads to an increased production of red cells. This is evident, not alone from the gradual rise in hemoglobin and in the erythrocyte count, but also from qualitative changes in the red cells, such as the occurrence of nucleated forms and of cells taking the basic stains. The new red corpuscles are usually deficient in hemoglobin, so that the restoration of color is not so rapid as the restoration of the number of red cells. The increased activity of the bone marrow following hemorrhage is responsible

for the leukocytosis and the increased platelet count which occur at this time.

Rapidity of Return to the Normal.—The time required for a restoration of the blood to the normal after a severe hemorrhage may be six weeks or more. The rapidity of this restoration depends not alone upon the severity of the hemorrhage but also upon the age of the individual, his general nutrition, the supply of iron, and the reaction of the bone marrow. In some cases there seems to be an overproduction of red cells and of hemoglobin, so that the total amount in the body rises above the normal level.

Repeated Hemorrhages.—Repeated hemorrhages are encountered most frequently in association with bleeding hemorrhoids, excessive menstruation, bleeding peptic ulcers, etc. The changes which follow repeated hemorrhages are in many respects similar to those which follow a single hemorrhage. If the hemorrhages are small, the hemoglobin in the body may be maintained at the normal level for long periods of time, owing to a compensatory increase in the regeneration. Indeed, the excessive regeneration may at times overcompensate the blood losses. If, however, the hemorrhages are severe and frequently repeated, the reparative processes tend to become exhausted, either from lack of new building material (iron) or from some fundamental change in the bone marrow cells. In such cases a severe and chronic anemia may become established.

Simple Toxic Anemias

We have seen that various poisons, which injure or destroy the red cells, may in large doses produce acute hemolysis, with hemoglobinemia, hemoglobinuria, jaundice, methemoglobin formation, etc. If the destructive action is less marked but more prolonged, the poisoning may cause anemia without other striking manifestations.

Lead Poisoning.—The anemia of lead poisoning, for example, is characterized by evidence of increased blood destruction and of increased activity on the part of the bone marrow. In a case examined by Eppinger and Charnas, large amounts of urobilin were found in the stools, which indicates an increased blood destruction. In lead poisoning a considerable number of the red cells in the peripheral blood may show basic staining granules. This change is believed to indicate immaturity and it suggests an increased activity on the part of the bone marrow. Why this increase in basophilic erythrocytes during lead poisoning is not accompanied by a corresponding increase in the number of nucleated forms is not known.

Infections.—The anemias which accompany various infections are usually regarded as being due to some toxic action upon the red corpuscles. In most cases, direct evidence in favor of this view is lacking, and it is probable that infections may also depress the formation of new cells

in the bone marrow. In certain patients suffering from infections diseases, however, there is direct as well as indirect evidence of increased hemolysis. Thus Wilbur and Addis found an increased urobilin excretion in a case of malignant endocarditis. Hemolysins have been obtained from certain bacteria (streptococci) and in some infections sharp attacks of hemolysis occur. The anemia of malarial fever is due in part to the disintegration of the infected corpuscles, but there is also evidence that the malarial parasites may produce hemolytic substances (see Blackwater Fever).

Malignant Tumors.—Malignant tumors may cause anemia partly through repeated hemorrhages and partly through interfering with the general nutrition of the body. They also contain hemolytic substances, and the blood sera of patients suffering from malignant disease show at times an unusual hemolytic action toward the red corpuscles of normal individuals.

Bothriocephalus and Hookworm.—Hemolytic substances have been isolated from the bodies of certain intestinal parasites, notably the bothriocephalus and the hookworm. The anemia which not infrequently accompanies infection with intestinal parasites is due in part to these hemolytic substances, in part to repeated small hemorrhages from the bowel (hookworm).

Megaloblastic Toxic Anemias

Experiments on animals have shown that anemias produced by certain toxic agents (phenylhydrazin, etc.) are accompanied by qualitative changes in the type of blood regeneration. Unusual numbers of nucleated and of basic staining erythrocytes appear in the peripheral blood, while abnormally large cells (megalocytes) or abnormally large cells with reticulated nuclei (megaloblasts) are also common. Such toxic anemias are, therefore, of the megaloblastic type. Examinations of the bone marrow in such cases also show a change in the character of the marrow cells which corresponds to that seen in the blood.

Pathogenesis.—The cause of this different type of blood regeneration is still under discussion. By some the difference has been attributed to an unusually active proliferation of cells in the bone marrow, the megaloblastic blood picture indicating that regeneration in the marrow is unusually active. In favor of this view is the fact that showers of nucleated red cells in the peripheral blood during the course of pernicious anemia are usually accompanied and followed by a rapid improvement in the anemia. By others the difference in type of blood regeneration is believed to be due, not to an increased functional activity alone, but to some direct damage of the blood-forming tissues. The intravenous injection of a hemolytic substance, for example, may cause a megaloblastic blood picture, whereas the subcutaneous injection of the same substance produces

a simple anemia. Possibly, in the former case, the toxic material directly damages the bone marrow. In chronic hemolytic jaundice the rate of red cell destruction may exceed that in pernicious anemia without the occurrence of a megaloblastic picture. This fact favors the view that the latter blood picture is due in part to some qualitative change in the blood-forming tissues. It therefore seems probable that the megaloblastic type of toxic anemia is due in part to direct damage to the bone marrow, and in part to an excessive new formation of red cells by this damaged and irritated tissue.

Pernicious Anemia

The cause of pernicious anemia is not known and for this reason it may properly be designated as a crytogenic anemia. The term primary as applied to pernicious anemia is objectionable, for the reason that there is every reason to believe that pernicious anemia is due to some unknown intoxication or infection; but the term serves the useful purpose of distinguishing this disease from those conditions in which a similar blood picture is produced by known causes. Ultimately, however, we may hope that the cause of pernicious as well as that of other so-called primary anemias will be found, and that with this finding these anemias will be classified according to their etiology.

Characteristic Changes.—The disease which has come to be known as pernicious anemia is characterized not alone by the changes in the blood to which so much attention has been given, but also by changes in other parts of the body and particularly in the nervous system and in the digestive apparatus. In patients suffering from this disease, free hydrochloric acid is almost invariably absent from the stomach contents. This achlorhydria may precede the anemia by many years, and it persists even when the blood picture becomes practically normal during remissions in the disease. According to Faber, it is accompanied by the anatomic changes of a chronic gastritis. Inflammatory conditions about the mouth (glossitis and stomatitis) are also common in pernicious anemia, and Hunter believes that these play a rôle in the pathogenesis of the disease. The diarrheas and other intestinal disturbances are similar to the intestinal complications of other types of achlorhydria.

NERVOUS SYMPTOMS.—Nervous symptoms occur in a large proportion of patients suffering from pernicious anemia. The milder and more common manifestations consist of paresthesias in the hands and feet. The more serious manifestations consist of paralyses, ataxias, and mental changes. The more serious nervous symptoms are caused by focal lesions in the spinal cord and brain. Like the achlorhydria, the nervous manifestations do not run parallel to the severity of the anemia, nor do they im-

prove with remissions in the blood picture. It is possible that the nervous changes may also, in some cases, antedate the development of anemia.

Relation Between Symptom Groups.—Apparently these three main groups of symptoms—the blood changes, the gastro-intestinal symptoms, and the nerve lesions—do not depend upon one another but are the result of a common cause. Their frequent association in pernicious anemia but not in other forms of anemia favors the view that this disease is a well-defined entity.

Increased Destruction of Red Cells.—In pernicious anemia there is an increased destruction of the red corpuscles. Iron containing pigments (hemosiderin) are deposited in the liver, the spleen and the kidneys. The slight yellow staining of the conjunctivae, the yellow skin and the brilliant yellow tint of the body fat are probably due to pigments derived from the destruction of the red cells. The amount of urobilin in the stools is usually increased and may be from three to ten times the normal. Urobilin is also frequently found in the urine, probably because it is absorbed in such quantity from the intestines that it passes through the liver into the general circulation. Just where or how the destruction of red cells occurs we do not know, although the remarkable reduction in the output of urobilin which sometimes follows splenectomy (Eppinger, Robertson) suggests that the spleen plays some rôle in the destruction of red cells in this disease. As a rule, no free hemoglobin can be demonstrated in the blood serum and hemoglobinuria rarely, if ever, occurs.

Activity of Bone Marrow.—In addition to the increased destruction of red cells in pernicious anemia there is also evidence of an unusual activity on the part of the bone marrow. Immature red cells are common in the peripheral blood, as is shown by the frequent occurrence of cells taking the basic stains, of cells with basic staining granules, and of nucleated red corpuscles. Qualitative changes in blood regeneration are indicated by the presence of large red cells (megalocytes) and of large nucleated cells with reticulated nuclei (megaloblasts). Pathological examination shows that the red bone marrow is more extensive than in health, and that it contains a relatively large number of immature cells. Extramedullary centers of new cell formation may also be found in the spleen, the liver and the other organs.

Possible Causes of Red Cell Changes.—Two explanations may be offered for the fact that both the destruction and the new formation of red cells are increased in pernicious anemia. In the first place, the new red cells may be in some way defective, so that they disintegrate in the blood with abnormal ease. In the second place, the increased new formation may be entirely secondary to an increased blood destruction and may, therefore, be regarded as a compensatory process. While a final answer as to the correctness of these possibilities cannot be given, it may be pointed out again that the blood picture in pernicious anemia cannot be

explained solely on the hypothesis of an increased destruction of red cells, for we know that in chronic hemolytic jaundice a much greater destruction may occur with no change to a megaloblastic type of regeneration.

Other Megaloblastic Anemias

We have seen that anemias of a megoblastic type may follow the introduction of certain toxic substances into animals. In man also the continued administration of certain drugs, and particularly of acetanilid, occasionally produces blood changes which resemble the blood picture of pernicious anemia. In addition to these toxic anemias of a megaloblastic type, a number of other similar anemias may occur in man where the etiology is more or less obscure.

Bothriocephalus Anemia.—The best studied of these is the pernicious type of anemia that is caused by the fish tapeworm, the *Bothriocephalus latus*. With the expulsion of the parasite, this anemia may disappear. A megaloblastic anemia occurs in only a small proportion of patients harboring this parasite, so that its occurrence appears to depend upon some contributing factor that is not yet known. The gastric achlorhydria which is practically universal in pernicious anemia is also common in the anemia produced by the bothriocephalus, being found, according to Tallqvist, in about 70 per cent of all cases.

A hemolytic substance has been isolated from the fish tapeworm, this being, according to Faust and Tallqvist, a cholesterin oleic acid compound. When this compound is split in the digestive tract, the oleic acid set free combines with alkalis to form soaps. Oleic acid and its soaps, like other unsaturated acids, cause hemolysis, and anemias have been produced experimentally by the administration of such acids to animals. As a rule, however, the resulting anemia has not been of a megaloblastic type, so that the relation of unsaturated fatty acids to bothriocephalus anemia and to typical pernicious anemia has not been satisfactorily demonstrated.

During Pregnancy and Confinement.—Anemias of a megaloblastic type also occur occasionally during *pregnancy* and in the *puerperium*. The clinical course of these anemias differs from that of pernicious anemia in that the disease usually runs an acute course and ends either fatally or with recovery. The exact cause of this anemia is not known.

In Other Conditions.—Pernicious types of anemia have also been described in association with syphilis, with malaria, and with a variety of other conditions. Such conditions usually produce simple anemias only and the occurrence of the pernicious form is so uncommon that it

may be a coincidence. Proof of an etiologic relation between the blood picture and these diseases could be demonstrated by showing that a complete and permanent recovery followed a removal of the supposed cause.

Pathogenesis of Pernicious Anemia

The fact that various poisons may produce anemias of a megaloblastic type both in animals and man suggests that pernicious anemia is also caused by the action of some toxic substance. Where this poison originates in the body and what is its nature have been subjects of much investigation, but as yet the pathogenesis of pernicious anemia is veiled in obscurity.

Digestive Tract.—In seeking a site of origin for the supposed toxic substance particular attention has been directed toward the *digestive apparatus.* Inflammations of the mouth and tongue are common in pernicious anemia and Hunter has laid particular stress upon such inflammations as etiological factors in the disease. The gastric achlorhydria which is present in nearly every case is certainly not a result of the blood changes, for: (1) it is often absent in other anemias of equal intensity; (2) pernicious anemia may develop in patients who have had achlorhydria for years (Faber); and (3) the achlorhydria persists during improvements in the blood picture. As a rule, the achlorhydria is regarded as coördinate with the anemia in the sense that both arise from a common cause. It is possible, however, that the achlorhydria may stand in an etiological relation to the disease. Achlorhydria permits the passage of unusual quantities of undigested material into the intestines, and bacteria from an infected mouth or from the food are not subjected to the antiseptic action of normal gastric juice. That hemolytic substances may be produced by these bacteria or by an unusual decomposition of material in the intestinal tract is possible but it is not proved. We know, furthermore, that the majority of patients with achlorhydria either have no anemia at all or have an anemia of the simple type.

Toxic Substances.—Nor are we any better informed concerning the *nature of the toxic substance* which is supposed to produce the anemia. In horses an anemia of the pernicious type occurs as an infectious disease, but efforts to prove the infectious character of pernicious anemia in man have thus far failed. Since a hemolytic substance of lipoidal character has been isolated from the fish tapeworm, efforts have been made to demonstrate that similar lipoidal substances are responsible for the hemolysis in pernicious anemia. Such substances have been extracted from the intestinal flora and from the intestinal mucous membrane of patients suffering from pernicious anemia, but they have been found in other conditions, so that their relation to the anemia is not established. King believes that a parallelism exists between the amount of

unsaturated fatty acids in the blood (oleic acid?) and the hemolysis observed in pernicious anemia and other hemolytic conditions. The observation is highly suggestive but it requires further confirmation and control. At the present time, therefore, despite the large amount of time and work which has been devoted to this problem, the pathogenesis of pernicious anemia remains unsolved.

Anemia from Defective Red Cell Formation

Poor general nutrition does not usually cause anemia. Even during prolonged periods of complete starvation, the number of red cells and the percentage of hemoglobin change but little. It is possible, however, that poor food and defective hygiene may lessen the resistance of an individual to other causes of anemia.

Deficiency of Iron.—A deficient amount of iron in the diet is rarely if ever the sole cause of anemia in adults. Although considerable amounts of iron compounds (100–200 mg.) are liberated daily as a result of the normal disintegration of the red cells, only very small quantities (6 mg.) are excreted, the major part being conserved for the formation of new hemoglobin. If, however, iron be lost from the body, as when anemia is produced by hemorrhage, a deficient supply of iron may become evident, for recovery from such an anemia is delayed unless adequate quantities of iron be taken in the food. Milk contains relatively small amounts of iron (2–3 mg. per liter). During the first year of life the infant makes good this deficit by using iron stored in his body. If, however, an exclusive milk diet be continued beyond the first year of life an anemia may develop from iron deficiency. According to Stöltzner, an iron deficit may in certain cases appear earlier than this; particularly when, as in premature infants or twins, there may have been a deficient supply of iron in the body at birth.

Bone Marrow Disease; Leukemia.—Disturbances in red cell formation may also result from a diffuse disease of the bone marrow. Such a disease may reduce the normal erythroblastic tissue or it may disturb its activities. In leukemia, for example, anemia is common and is apparently caused by the exuberant growth of the cells which give rise to leukocytes, thus interfering with the growth of the erythroblastic tissues.

Aplastic Anemia

In the rare disease known as aplastic anemia the red bone marrow is so reduced in extent as to be almost absent. This condition is characterized by a severe anemia without the appearance of immature erythrocytes in the peripheral blood, by a leukocyte count of 2,000 or less owing to a reduction in the granular leukocytes, and by a tendency to hem-

orrhages (lack of platelets). The rate of red cell production is usually diminished, and evidences of an increased rate of erythrocytic destruction are usually absent. In a few cases, however, abnormal deposits of iron have been found in the internal organs. This anemia, therefore, appears to be due to a failure on the part of the bone marrow which may be, but usually is not, accompanied by evidences of increased destruction.

Produced by Experiment in Animals.—This type of anemia has been produced experimentally in animals by certain poisons which damage the bone marrow, such as saponin and benzol.

Secondary Aplasia.—Aplasia of the bone marrow occasionally complicates other types of anemia, both hemorrhagic and toxic. In such cases, it appears to represent a secondary condition of exhaustion or damage which results in a failure of regeneration. This secondary aplasia is probably distinct from the true aplastic anemias in which the bone marrow aplasia is the primary cause of the blood changes.

Milder Forms.—Of the milder forms of bone marrow aplasia we know almost nothing. It is not improbable, however, that various anemias in which no excessive blood destruction has been demonstrated may depend on a slight failure of bone marrow activity. Certain anemias associated with infectious diseases and malignant tumors may possibly arise in this way.

Chronic Hemolytic Jaundice

We have seen that acute attacks of hemolysis may cause a transient jaundice owing to the formation of large quantities of bile pigment from the liberated hemoglobin. A chronic increase in the rate of red cell destruction may cause an analogous, but chronic, jaundice. This rare condition (chronic hemolytic jaundice) may occur as a family disease, or it may be acquired.

Family Hemolytic Jaundice

This remarkable disease, to which attention was first directed by Hayem and by Minkowski, presents a well-defined clinical entity which is characterized as follows: (1) the child is usually born jaundiced or becomes so shortly after birth; (2) this jaundice may persist for years with no apparent impairment of health and no shortening of life; (3) the spleen is enlarged; (4) bile pigments are present in the stools and in the blood but are absent in the urine, the dark color of the latter being due to urobilin; and (5) the condition is a family disease.

Excessive Red Cell Destruction.—In such patients there is no gross obstruction in the bile passages and the liver appears normal. The jaundice is due to an increased destruction of red blood corpuscles in the body. Clinically this is evident from the extraordinary quantities of urobilin

that appear in the stools. According to Eppinger and Charnas, this may be as high as 20 to 30 times the normal. Considerable urobilin also appears in the urine. Pathologically the excessive blood destruction is evident from the large deposits of iron free pigment in the liver and spleen and the smaller deposits of iron-containing pigment in the spleen and kidney. It is obvious that with such an increased destruction of red cells there must be a corresponding new formation. Signs of increased regeneration are found on examination of the blood films from such patients. The red cells show polychromasia and basophilic granulations, and nucleated forms, both normoblasts and to a lesser extent megaloblasts, may be present in varying numbers. Vital staining of the red cells shows a peculiar granular filamentous structure of many cells which is also evidence of immaturity.

HEMOLYTIC CRISES.—In this type of hemolytic jaundice, crises of increased red cell destruction may occur. During these the jaundice deepens, the swelling of the spleen increases, and there may be hemoglobinuria or acute attacks of pain either in the splenic or hepatic regions. After such crises there is a fall in the hemoglobin and in the number of red cells.

Acquired Hemolytic Jaundice

The acquired type of hemolytic jaundice appears to be rare and it does not present such a well-defined clinical syndrome as the family type. In some cases it appears to be associated with syphilis, malaria or carcinomata, in other cases no cause is apparent. The clinical manifestations: jaundice with increased urobilin in the stools and urine, anemia, splenic tumor and hemolytic crises, are similar to the manifestations of the family form of the disease. The anemia is at times a more marked manifestation than the jaundice, so that transitions occur to cases of splenic anemia with increased blood destruction.

Pathogenesis

The cause of the remarkable hemolysis in these conditions is not certain. Chauffard showed that in the family type of the disease the red corpuscles were unusually susceptible to hemolysis by dilute salt solutions; their fragility was increased. Hemolysis by other agents, such as weak acids and sera, may also occur with unusual ease, whereas hemolysis with other toxic substances, such as saponin, may not differ from the normal. In the acquired type of hemolytic jaundice the corpuscular fragility is usually less affected. Possibly some defect in the red cells represents the primary cause of the disease, particularly in the family type. Hemolytic

substances have been looked for repeatedly in the sera of these patients, but as a rule they have not been found.

Enlargement of Spleen.—The enlargement of the spleen in hemolytic jaundice has been variously interpreted. By some it is regarded as a secondary manifestation, being due to a collection of cellular detritus in this organ. By others the spleen has been assumed to take an active part in the hemolytic processes. The fact that excision of the spleen has at times been followed by a lessened excretion of urobilin in the stools and by an improvement in the anemia favors the second view.

The Relation of the Spleen to Anemia

Enlargement of the spleen occurs in various blood diseases. In leukemia it is due to the increased number of white cells in this organ, and in certain anemias areas of red cell proliferation may be present. After hemolysis from various causes the spleen contains considerable detritus derived from disintegrated or destroyed corpuscles. It is certain that these may be in part the result of a mechanical and phagocytic filtration of the detritus out of the blood, and that the spleen acts as a graveyard for damaged red cells. Of more importance, however, are the questions as to whether the spleen plays an active rather than a passive rôle in the destruction of red cells, and whether it is a primary or contributing factor in the pathogenesis of certain forms of anemia. To solve this question numerous studies on patients and on animals have been carried out.

Effect of Splenic Excision on Normal Animals

The spleen is not an organ which is essential to life and it may be removed from men as well as from animals without serious consequences. Following its removal from dogs there develops an anemia which usually reaches its height in from three to six weeks, after which the blood gradually returns to the normal. A leukocytosis develops within the first twenty-four hours after splenectomy and this may persist to a slight extent for months. The cause of the anemia which follows removal of the spleen from normal animals has not been determined. While Pugliesi and Gauckler maintain that the secretion of bile is reduced to one-half or less after splenectomy, Paulesco was unable to obtain a similar result. It is, therefore, possible, but not certain, that in normal animals excision of the spleen diminishes blood destruction. If this were so, the anemia could only be due to a diminished activity of the blood-forming tissues. Of this there is no evidence, and Pearce and Pepper found that while the bone marrow was not markedly changed during the first two or three months following splenectomy, there was ultimately an increase in the red marrow at a time when the anemia had improved.

Fragility of Red Corpuscles.—Excision of the spleen from animals is followed by an increase in the resistance of the red corpuscles to the action of hypotonic salt solution and to that of various hemolytic agents. Pearce and his coworkers have attributed this increased resistance to the anemia and have shown that a similar increase may occur when anemia is produced in other ways.

Effect of Toluylendiamin Injection.—The injection of toluylendiamin into normal animals produces a hemolytic anemia with jaundice. W. Hunter, Banti, Joannovics and others have shown that splenectomized animals are peculiarly resistant to this action of toluylendiamin. Jaundice is less easily produced, the anemia following the injection is less marked, and deposits of iron-containing pigments in the liver and bone marrow may be absent. Toluylendiamin does not dissolve red corpuscles in vitro and its injection into the body must, therefore, lead to changes in the tissues or fluids whereby red cell destruction and jaundice are favored. The increased resistance of splenectomized animals to toluylendiamin injections suggests that the spleen plays some important rôle in the hemolysis caused by this poison.

Splenic Anemia and Related Conditions

Splenic anemia, described by Banti in 1882, is characterized by a considerable splenomegaly, a severe progressive anemia, and by recovery after a successful extirpation of the spleen. The condition known as Banti's disease is analogous to splenic anemia but there is here in addition an atrophic hepatic cirrhosis. In this condition also splenectomy may be followed by an improvement of the anemia and by an arrest of the hepatic cirrhosis.

Changes in the Splenic Vein.—Changes in the splenic vein are common in these diseases. They assume considerable clinical interest, partly because they may be responsible for the severe gastric hemorrhages that frequently complicate these conditions, and partly because the sclerotic veins add to the technical difficulties encountered by the surgeon who undertakes to remove the spleen. These changes in the splenic vein may possibly be due to changes in the blood coming from the spleen. Possibly, however, as Dock and Warthin have pointed out, a thrombophlebitis of the splenic and portal veins may cause or contribute to the clinical picture.

Relation of Enlarged Spleen to Blood Changes.—The relation of the enlarged spleen to the blood changes in splenic anemia is not altogether certain, but in view of the recoveries after splenectomy it seems fair to assume that the enlarged spleen plays an important rôle in producing the anemia. Increased hemolysis has not been demonstrated in all of these

cases. To the cases associated with jaundice Banti has given the name of hemolytic splenomegaly.

Effect of Splenectomy upon Pathological Hemolysis

In certain diseases of the blood associated with evidence of increased destruction of red cells, splenectomy may be followed by prompt improvement and by evidence of diminished hemolysis. This is true, for example, in chronic hemolytic jaundice and in the type of splenic anemia that is associated with increased hemolysis. More recently, splenectomy has been advocated in the treatment of pernicious anemia by Eppinger and others. The immediate improvement following this operation is at times striking; and Eppinger, Robertson and others have shown that the operation may be followed by a definite and marked reduction in the amount of urobilin excreted:

EFFECT OF SPLENECTOMY ON UROBILIN EXCRETION
(After Eppinger)

Disease	Urobilin in Stool Before Splenectomy	Urobilin in Stool After Splenectomy
Normal	0.13	....
Hemolytic Jaundice I	2.96	0.062
Hemolytic Jaundice II	3.95	0.070
Pernicious Anemia I	0.276	0.03
Pernicious Anemia II	0.65	0.015
Banti's Disease	0.36	0.05
Hypertrophic Hepatic Cirrhosis	0.413	0.08

Results in Pernicious Anemia.—The results obtained indicate that in pernicious anemia as well as in chronic hemolytic jaundice the spleen plays some rôle in the pathological destruction of the red corpuscles. The results in pernicious anemia, however, have not been uniformly good. In some cases no improvement either in the clinical manifestations or in the amount of urobilin excreted has followed the operation and, as a rule, the improvement following splenectomy has not been permanent. It seems probable, therefore, that in pernicious anemia the spleen is not the sole site of hemolysis, and that its removal, while beneficial in certain cases, cannot be counted on to cure the disease.

Chlorosis

Chlorosis occurs mainly, if not exclusively, in young women. The occurrence of the disease in men or in children is doubtful. The disease usually develops about the time of puberty, between the ages of 14 and 20. Once having developed, however, relapses may occur beyond these ages. Patients suffering from chlorosis are pale but are commonly well nourished. They suffer from the usual symptoms of anemia; weakness, dyspnea on exertion, and fatigue. Not infrequently they are constipated

and suffer from menstrual disturbances. The administration of iron preparations usually causes a striking improvement in the anemia and an amelioration of all symptoms.

Blood Picture.—The blood picture of chlorosis is characterized by an unusually low color index. While the number of red corpuscles is normal or but moderately reduced, the hemoglobin falls to 50 per cent or less. The red cells appear pale, the white cells are not definitely changed, and the platelets tend to be increased.

Etiology.—The cause of chlorosis is not known. The fact that it occurs mainly, or possibly exclusively, in women at about the time of puberty suggests that it depends in some manner upon the development of the sexual functions of the female sex. Beyond this, however, we know nothing. The anemia does not appear to depend upon an increased destruction of erythrocytes, for the urobilin in the stools is not increased and pigmentations are rare. Nor is there any marked evidence of increased proliferation on the part of the red cells, for basophilic cells and nucleated cells are uncommon. It seems probable, therefore, that the immediate cause of the blood picture is some alteration in the formation of red cells in the bone marrow.

Blood Volume.—According to Lorain Smith and to Plesch, the quantity of blood in the body of chlorotic patients is increased. Using the carbon monoxid method, Smith determined the blood volume in thirty chlorotic patients and found that this volume was regularly increased in the severe types of the disease, and that the increase was approximately proportional to the reduction in the percentage of hemoglobin. It would appear from these determinations, therefore, that the total quantity of hemoglobin in the blood of chlorotic patients approximates the normal, while the total number of red cells in their blood is greater than the normal. Smith found, furthermore, that with an improvement in the anemia the total quantity of blood in the body returned to the normal. Possibly this accounts for the observation that the weight of chlorotic patients may fall during rapid improvements under iron medication.

Blood Volume in other Anemias.—The marked increase in the blood volume of chlorotic individuals, as demonstrated by the carbon monoxid method, is of no little interest and it is to be hoped that these findings will be tested by other methods for determining the blood volume. It is possible that in other blood diseases also variations in the blood volume may cause us to modify our conception as to the character of the blood changes. We have seen, for example, that in posthemorrhagic anemias there may be an increase in the blood volume which compensates for the reduced percentage of hemoglobin. Carbon monoxid determinations indicate that this also occurs in the anemia produced by the ankylostoma, whereas in pernicious anemia there is an actual reduction in the total hemoglobin in the body. The following table, taken from Boycott's

article, illustrates the relation of the blood volume (carbon monoxid method) to certain blood diseases:

BLOOD VOLUME AND TOTAL HEMOGLOBIN IN CHLOROSIS AND OTHER BLOOD DISEASES

	Blood per K	Hb per cent	Hb gm per K	RBC Millions per c.mm.	Total RBC	Color Index
Normal Average	50	100	6.7	.....	...	....
Congenital Heart Disease	131	180	33.0	.....	...	....
Splenomegalic Polycythemia	97	148	20.0	.....	...	....
	160	176	37.0	.....	...	....
Normal Women	50	90	6.7	4.5	100	1
Chlorosis	105	47	6.9	4.0	187	0.58
	128	38	6.7	3.4	193	0.56
	143	32	6.5	2.6	165	0.61
	73	40	5.7	4.3	140	0.46
	86	58	6.9	3.6	138	0.80
Normal	50	100	6.7	.....	...	....
Ankylostomiasis	86	44	5.2	.....	...	....
	92	47	6.0	.....	...	....
	98	41	5.5	.....	...	....
Normal	50	100	7.0	5.00	100	1.00
Pernicious Anemia	49	43	3.4	1.62	32	1.35
	76	32	3.0	1.10	33	1.45
	49	26	1.7	1.05	20	1.24
	106	17	2.5	0.625	26	1.33
	117	15	2.3	0.50	24	1.50

Polycythemia

Classification

Polycythemia, or an increase in the number of red corpuscles or in the amount of hemoglobin to the unit of blood volume, may be due to a number of causes.

Relative Polycythemia.—In this form, there is no absolute increase in the number of red cells nor in the amount of hemoglobin in the body. The change that is evident on an ordinary blood examination is due to a concentration of the blood, owing to a reduction in the amount of plasma. Such a reduction may be general throughout the body or it may be local. General reductions may result from marked losses of fluid, such as occur in copious diarrheas, profuse sweats, or marked diuresis. Polycythemia may also be due to local causes. This happens, for example, when the veins from an extremity are obstructed and more fluid passes out of the peripheral capillaries. Possibly vascular changes of various kinds may produce similar alterations in the concentration of red corpuscles in the blood.

True Polycythemia.—In the true polycythemias, on the other hand,

there is not only an increase in the number of red corpuscles to the unit of blood volume, but the total number of corpuscles and the total amount of hemoglobin in the body are also increased. In such patients, indeed, the blood volume may be greater than normal, so that the total number of red cells in the body is even greater than the count indicates. In some cases of polycythemia, the condition is evidently dependent on other pathological changes. It is, therefore, a secondary or symptomatic polycythemia. In other cases, the cause of the blood change is not known, and these have been described as primary, essential, or cryptogenic polycythemias. As with anemias, however, the latter group will tend to diminish in number as our growing knowledge enables us to recognize the various causes of the blood change.

Symptomatic Polycythemias

Cyanosis

It has long been known that the cyanosis of congenital heart disease is usually associated with an increased number of red cells to the unit of blood volume. Intense cyanosis in other cardiac conditions, though less common, may at times be associated with a moderate polycythemia. In the marked cyanosis which characterizes the circulatory failure in pulmonary emphysema, the red cell count may also be markedly increased. Sclerosis of the pulmonary artery and of its branches may lead to high grade cyanosis and polycythemia. In such conditions blood counts of 9,000,000 and over have been reported, while the hemoglobin may rise considerably above 100 per cent. That such conditions are not due simply to a lessened amount of blood plasma is evident: (1) from the fact that the red bone marrow may be more extensive than usual; and (2) from the fact that determinations of the blood volume have shown that this is either normal or increased. Thus Lorain Smith and McKisack observed a child with marked cyanosis due to adherent pericardium in whom the red cells were increased to about six millions while the blood volume as determined by the carbon monoxid method was about twice the normal.

Altitude

The red cell count is regularly increased in men as well as in animals who live at very high altitudes. In the higher Andes, for example, counts of 7 to 8 millions are normal. The cause of such high counts has been a subject of numerous investigations. Some have maintained that the blood changes are purely relative, being due to losses of liquid from the body or to vasomotor influences. Others have maintained that there is an actual increase in the total number of red cells in the body. It seems probable that both factors play a part in producing the polycythemias that have

been observed at high altitudes. In some individuals the red cell count increases promptly when a change is made to a high altitude, and decreases just as promptly if the return to sea level is made after a short stay. Indeed it has been claimed that during a prolonged balloon ascension the red cell count may be temporarily increased. Such sudden changes probably depend upon variations in blood concentration, and they have been attributed to losses of liquid and to vasomotor disturbances.

Absolute Increase in Red Cells and Hemoglobin.—On the other hand, it now seems definitely established that a prolonged residence at high altitudes leads not only to an increase in the blood count, but also to an increase in the total number of red cells and the total amount of hemoglobin in the blood, for the blood volume is normal or increased. This increase in hemoglobin at high altitudes may be regarded as one of the compensatory processes which enables the inhabitants of mountainous regions to overcome the physiological disturbances produced by a low oxygen tension (see Respiration at High Altitudes).

Intoxications

Polycythemia has also been observed after the action of various poisons. As a rule, the poisons which produce this effect either damage the red cells or interfere with the carrying or utilization of oxygen in the body. Among the toxic substances that may at times produce polycythemia are arsenic, phosphorus, carbon monoxid, and small doses of certain hemolytic poisons, such as toluylendiamin and acetanilid.

Cryptogenic Polycythemias

The cryptogenic type of polycythemia is usually associated with general cyanosis and a marked enlargement of the spleen (Vaquez's disease, Osler's disease). If the skin circulation becomes markedly accelerated, owing to exposure to heat, the cyanotic color may change to a bright red. The mucous membranes present a violet color and the retinal veins are congested and tortuous, so that the ophthalmoscopic picture is suggestive of the condition.

Increased Number of Red Corpuscles.—The number of red corpuscles is increased. Counts of from 7 to 10 million are common, and in exceptional cases counts of 15 million or even more have been reported. The increase in hemoglobin is usually less marked than the increase in the number of red cells, thus producing a color index of less than 1.0. The total blood is often increased, and by the carbon monoxid method increases of from one and a half to three times the normal have been determined. The increased quantity of blood has also been remarked at autopsy, for unusual amounts escape from the heart and veins. There is, therefore, a

true plethora, and the ordinary blood examinations fall short of indicating the actual increase of red cells and of hemoglobin in the body.

Clinical Symptoms.—Among the clinical manifestations, cerebral symptoms are common. Of the cases collected by Lucas, 31 per cent complained of headache and about 34 per cent of vertigo. Increases of blood pressure have also been rather frequent, as may be seen from his collected statistics:

Blood Pressure	Number of Cases
Below 140	21
145–170	23
180–200	13
200 and over	9

The cases with high blood pressure frequently show no splenic enlargement, and it has been suggested that they should be placed in a separate group from the cases with normal blood pressure and splenomegaly.

Pathogenesis of Polycythemia

As in other blood conditions, the number of red cells destroyed must equal the number formed, so long as the blood picture remains stationary. Under such circumstances, an increase in the total number of red corpuscles in the body may be produced: (1) by a longer life of the individual red cells in the blood; (2) by a more rapid rate of regeneration and destruction; or (3) by a combination of the two processes. In most cases the rates of erythrocytic production and destruction in polycythemia appear to be increased. In the cases examined by Eppinger and Charnas, the urobilin output in the stools was increased, and urobilin has often been found in the urine. Basic staining red corpuscles and nucleated red cells have been found in a considerable proportion of the cases. Occasionally large numbers of nucleated red cells and even of megaloblasts have been reported. The leukocytes may also be increased. In many, but not in all cases, the red bone marrow has extended beyond its usual confines.

Increased Production and Destruction of Red Cells.—It seems evident, therefore, that in many cases of polycythemia there is an increase in the rate of red cell proliferation and of red cell destruction. In the two cases examined by Eppinger and Charnas, for example, the urobilin excretion in the stools (0.50 and 0.89 g.) was four to seven times the normal (0.13 g.). If the average life of the red corpuscle was not altered, such an increase in red cell destruction and formation would cause a corresponding increase in the total number of red cells in the body. Since the red cell count in these cases, 7,100,000 and 8,500,000, respectively, indicated that the number of red cells in the body fell short of this estimate, it seems probable that in these cases at least a prolongation of the life of the individual cell played no part in the production of the polycythemia. The overproduction of red cells appears to be primary, the over-

destruction, in part at least, a secondary result. On the other hand, Wilbur and Addis report a case of cryptogenetic polycythemia in which there was no increase in urobilin output, and occasional cases have been observed in which at autopsy no evidence of change in the blood-forming organs was found. Possibly in these cases the polycythemia was due to an unusually prolonged life of the red corpuscles.

Diminished Oxygen Supply.—The stimulus that leads to an overproduction of red cells in certain cases is not definitely known, but it has been suggested that in certain forms of symptomatic polycythemia there may be some deficiency in the oxygen supply to the tissues, and particularly to the bone marrow. This is true, for example, of the cyanosis accompanying congenital heart disease and advanced pulmonary emphysema, of life at high altitudes, and of carbon monoxid poisoning, in which last condition a portion of the hemoglobin is rendered useless for respiratory purposes. In phosphorus poisoning, also, there seems to be a change in the tissue metabolism which interferes with the utilization of oxygen (see Acidosis, Lactic Acid). Apparently the bone marrow reacts to a deficient oxygen supply by an increased production of red cells.

After Giving Hemolytic Poisons.—Other types of symptomatic polycythemia have followed the administration of hemolytic poisons, such as toluylendiamin or acetanilid. In the anemias produced by such toxic substances the formation of red cells is also increased, but the increase is not sufficient to compensate for the shortened life of the average erythrocyte. It seems probable that under certain conditions, and especially when small doses are given, the reaction on the part of the bone marrow may be excessive, so that despite the briefer life of the red cells their number in the blood is increased.

Cryptogenic Type.—The pathogenesis of cryptogenic polycythemia is not known. Attempts have been made to separate it entirely from the secondary types of the disease, comparing it with leukemia (erythremia) rather than with the leukocytoses (erythrocytosis). It is true that the cryptogenic type of polycythemia is, on the whole, more intense, that the spleen is more commonly enlarged and that the prognosis is relatively unfavorable. But these appear to be differences in degree rather than in kind, and the symptomatic form may in some cases present all the clinical features of the cryptogenic form, save that its etiology is known. Furthermore, Pappenheim points out that the marrow changes in cryptogenic polycythemia are in no way comparable to those observed in leukemia. The overproduction of red cells is usually of a normal type and it is quantitatively less, for example, than that which occurs in chronic hemolytic jaundice (urobilin determinations). There seems no reason for separating the various forms of polycythemia in such a fundamental way. At the present time, therefore, it seems advisable to classify them as secondary when the etiology is known, and as cryptogenic when it is unknown.

The Transfusion of Blood

The possible advantages that might accrue from the transferal of blood from a healthy animal or man to a sick patient were recognized by the older generation of physicians; but the serious or even fatal consequences that occasionally occurred during such transferals caused the method to be discarded. With our increased knowledge of the nature of these dangers, however, it has become possible to avoid them. For this reason the transfusion of blood has assumed great practical value in the treatment of certain diseases. Various phenomena associated with the introduction of blood into an animal have been discussed in previous pages, but it seems advisable to bring these together in the present place.

Dangers of Transfusion

(*a*) *Hemolysis*

Blood cannot be safely transferred from one animal to another belonging to a different species. The blood serum of one species often hemolyzes the corpuscles of another, and even though such hemolytic properties are absent, they frequently develop in response to repeated injections of foreign red cells. For this reason successive injections of foreign blood become increasingly dangerous (see Hemolysis). Even among animals belonging to the same species hemolysins may, in certain instances, be developed by repeated blood injections (isohemolysins).

Avoidance by Preliminary Tests.—It is said that hemolysis never occurs when the sera and corpuscles from normal men are mixed; but isohemolytic substances may probably develop in certain instances on repeated injections, and hemolysis may certainly occur when sera or corpuscles from diseased persons are used. A blood transfusion for the treatment of disease may, therefore, be followed by an acute hemolysis, with hemoglobinuria and even death. This acute hemolysis may be anticipated and prevented, however, by a preliminary examination of the reaction that takes place in a test tube between the blood of the patient and the blood of the proposed donor. Experience has shown that where no hemolysis occurs in the test tube no danger from intravascular hemolysis after transfusion need be feared.

(*b*) *Agglutination*

Agglutination of the red cells of one individual by the serum of another is far more common than is hemolysis. When hemolysis occurs, moreover, it is usually preceded or accompanied by agglutination. Moss has classified individuals according to the agglutinative properties of their sera and red cells as follows:

Group I. Sera agglutinate no corpuscles.
Corpuscles agglutinated by sera of all other groups.

Group II. Sera agglutinate corpuscles of I and III.
Corpuscles agglutinated by sera of III and IV.

Group III. Sera agglutinate corpuscles of I and II.
Corpuscles agglutinated by sera of II and IV.

Group IV. Sera agglutinate corpuscles of all other groups.
Corpuscles agglutinated by no sera.

Within each group no agglutination and no hemolysis occurs when the sera and corpuscles of different individuals are mixed. Transfusion from one to another individual within a given group is, therefore, perfectly safe so far as any dangers connected with these phenomena are concerned.

Danger from Agglutination.—The actual danger associated with transfusion in those cases where the serum of the donor possesses agglutinative properties toward the corpuscles of the recipient is not great, for the amount of serum received is relatively small, and it is usually not present in sufficient concentration within the body of the recipient to agglutinate his corpuscles. When, however, the serum of the recipient agglutinates the corpuscles of the donor, it seems probable that agglutination may occur within the body of the recipient. Even here, however, accidents appear to have been rare; although the remarkable phagocytosis of (foreign?) red cells observed after certain transfusions may have been dependent upon the sensitization of the foreign corpuscles by such agglutinative substances.

(*c*) *Coagulation and Protein Intoxications*

The injection of various substances into the blood vessels may cause fever and intravascular clotting (see Causes of Fever, Thrombosis). Defibrinated blood has, in certain cases, caused intravascular thrombi. The substance responsible for this change is not fibrin ferment, for large quantities of pure ferment may be injected into animals with impunity. On the other hand, substances that contain thrombokinase, or that lead to a liberation of thrombokinase by destruction of the formed elements of the blood, may cause intravascular thrombi. When defibrinated blood is used for transfusion it has been claimed that the dangers of clotting may be minimized by taking care not to squeeze the fibrin taken from the blood and by allowing the defibrinated blood to remain in an ice chest for 24 hours previous to making the injection.

Use of Uncoagulated Blood.—Modern technic has greatly lessened this danger by making it possible to use uncoagulated blood. The latter may be introduced: (1) directly by anastomosing superficial blood vessels

of the recipient and donor (Crile); (2) by injecting blood immediately after it has been withdrawn from the blood vessels (Lindeman); or (3) by preventing clotting with small amounts of sodium citrate (Weil).

Effect of Foreign Proteins.—Not infrequently a group of symptoms follow the transfusion of blood which are similar to those produced by the injection of foreign proteins into the body (see Anaphylaxis). Among these symptoms are fever and skin eruptions of an urticarial nature. Such symptoms appear to be particularly marked and frequent when defibrinated blood is used.

Beneficial Effects of Transfusion

The beneficial effects of blood transfusions are due in part to the increased amount of fluid introduced into the vessels. In this regard they probably possess no advantage over the injection of normal saline solution.

The Introduction of Red Cells.—The second cause of benefit depends upon the introduction of red cells. In anemias from various causes and in poisoning from illuminating gas the beneficial effect of such an addition of red cells is obvious. It seems certain, however, that the red cells introduced into the body do not live very long. The life of the

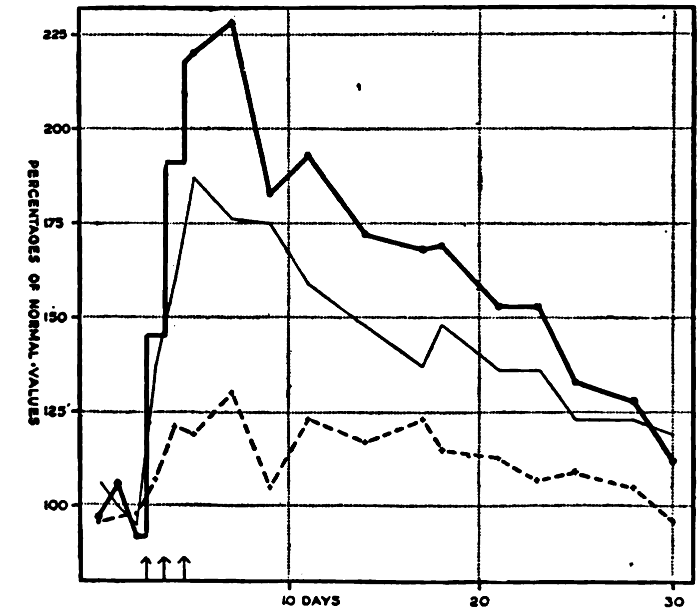

Fig. 124.—Effect of Repeated Transfusions of Blood Upon the Hemoglobin and Blood Volume of a Rabbit. The Thin Line Represents the Percentage of Hemoglobin, the Broken Line Represents the Blood Volume, and the Heavy Line Represents the Total Amount of Hemoglobin in the Body. Note that As a Result of the Transfusions There Is a Slight Increase in the Total Amount of Blood in the Body and a More Marked Increase in the Percentage and Total Amount of Hemoglobin. The Effect Lasted for Over Thirty Days. (From Boycott and Douglas, Jour. Path. and Bacter.)

normal red cell is from ten to twenty days, and it is probable that the life of foreign cells is less. Todd and White, who followed the fate of the cells injected by biological methods of study, were able to demonstrate these cells for from four to nine days after the injection. After large transfusions into normal animals the quantity of hemoglobin in the body may be increased for twenty days or more (Fig. 124). While the life-saving effects of blood transfusions are thus easily explained in such conditions as acute hemorrhage or carbon monoxid poisoning, it is evident that some other explanation is required for the prolonged improvement which may follow blood transfusion in such chronic conditions as pernicious anemia. Morawitz has suggested that the foreign blood, even in small quantities, may exert some stimulating effect upon the processes of regeneration in the bone marrow.

Beneficial Effect in Hemorrhagic Diseases.—Remarkable improvement has followed the transfusion of blood into patients suffering from various hemorrhagic diseases, such as hemophilia, purpura hemorrhagica, melena neonatorum, etc. The mechanism of the improvement in these various types of hemorrhagic disease probably varies according to the character of the disease, but it is evident from the prompt cessation of hemorrhage in many cases that the foreign blood supplies some element which prevents further hemorrhage.

Pathology of the Leukocytes

Classification and Origin

Classification

The white corpuscles of normal human blood are distinguished from one another partly by the shape and staining properties of their nuclei and partly by the amount, staining properties, and granulations of their protoplasm. They fall into two main groups: the non-granular mononuclear cells and the granular polynuclear (polymorphonuclear) cells.

Non-granular Cells.—To the first group belong the typical *lymphocytes.* These are small to medium-sized cells, having a single, small and deeply stained nucleus, which is surrounded by a narrow or broad band of basic-staining protoplasm. The nucleus is usually round, but it may be somewhat flattened or indented. These cells make up about 23 per cent of the total leukocytes of normal blood.

In the first group also we may place the *large mononuclear cells,* which are characterized by their large size, the round or somewhat irregular character of their nuclei, and the relatively good staining of nucleus and protoplasm. The nature and relationship of these cells are at present uncertain, for while some have allied them with the lymphocytes, others

have allied them with the transitional cells. Certain ancestors of the granular forms resemble in appearance the large mononuclears, but it seems improbable that these appear normally in the peripheral blood stream. The large mononuclear cells make up from 2 to 4 per cent of the total leukocyte count.

Granular Polynuclear Leukocytes.—The polynuclear leukocytes with protoplasmic granulations are divided into three main groups according to the character of the granulations. The most numerous are those containing fine granules which take the neutral stains, the *neutrophils.* These make up from 65 to 72 per cent of the leukocytes in normal human blood. Next in number come the polynuclear cells, which contain large, round and highly refractile protoplasmic granules. These cells, the *eosinophils,* make up from 2 to 4 per cent of all leukocytes. Finally, we have cells with large, irregular granules which take a deep basic stain, the *mast cells.* The last make up less than one per cent of the total leukocyte count.

Transitional Cells.—All of the leukocytes thus far described are now regarded as mature cells in the sense that transitions do not occur from one form to another in the peripheral blood. The so-called *transitional cells* are large cells with a single indented or lobed nucleus and with an abundant protoplasm, containing very fine granules which take basic stains. It seems certain that these cells do not represent a transition between the large mononuclear cells and the polynuclear neutrophils. Some observers have held that the transitionals are related to the large mononuclears, others that they are related to the parent cells of the polynuclear neutrophils (myelocytes), while still others believe that they are to be distinguished from both.

Origin

Polynuclear Cells.—Both neutrophilic and eosinophilic cells originate normally in *the bone marrow,* and they have, therefore, been called the myeloid cells. Their immediate ancestors, the *myelocytes,* possess the characteristic granulations, but their nuclei are round or oval. As the myelocytes become older the nucleus becomes more deeply indented (kidney and horseshoe shapes) and eventually it is broken up into several fragments, often united by fine filaments of nuclear material. The age of granular cells is, therefore, indicated by the degree of nuclear lobulation. Arneth has proposed that these cells be further classified according to the number of nuclear fragments which they contain.

The myelocytes, both neutrophilic and eosinophilic, are derived in turn from large bone marrow cells which have a non-granular, basic standing protoplasm and a round nucleus (*myeloblasts*). In the development of granular leukocytes, therefore, we have originally a large mononuclear and non-granular cell which first develops protoplasmic granules and later a lobulation of its nucleus.

Mononuclear Cells.—The lymphocytes of the peripheral blood take their origin from the small lymphatic cells that are found in *lymphatic tissues* through the body. The origin of the large mononuclear and transitional cells is still uncertain.

Ultimate Ancestry of Blood Cells.—While most hematologists believe that the immediate ancestry of the various blood cells is distinct and that transitions do not occur between the main types, it is possible that at a very early period the cells of the blood may all have arisen from a common ancestral cell. In pathological studies, however, the changes observed may, as a rule, be correlated with the immediate ancestry of the cells and the ultimate origin is rarely of clinical interest.

Some Biological Properties of the Leukocytes

Chemotaxis

The white blood corpuscles show ameboid movements. These are particularly evident in the case of the neutrophils, are somewhat less marked in the case of the eosinophils, and are very slight and slow in the case of the lymphocytes. The last, indeed, are often regarded as non-ameboid cells. The direction in which the leukocytes move is governed mainly by the chemical constitution of the medium that surrounds them. Bacteria and foreign proteins usually exert an attractive influence (positive chemotaxis) upon the neutrophils, and when introduced into the body they often become surrounded by large numbers of these cells. The part played by such cells in the processes of infection and immunity has been discussed elsewhere (see Phagocytosis). It will be recalled that such local collections of leukocytes are often associated with an increased number of the corresponding cells in the circulating blood.

Just as bacteria and their products usually exert a positive chemotactie influence upon the neutrophilic leukocytes, so the material from trichinae and other parasitic worms is believed to exert a similar attractive influence upon the eosinophilic cells. To what extent chemotactic substances are responsible for collections of lymphocytes is less certain.

Ferments

The white cells in the blood like cells elsewhere in the body possess a variety of ferments. These ferments may be liberated after death of the cells or possibly they may be secreted during their vital activities. The ferment content of the different leukocytes varies. Neutrophilic cells contain an oxidizing ferment and also contain a powerful proteolytic ferment, which, like trypsin, is most active in neutral or slightly alkaline solutions. Lymphocytes, on the other hand, possess a proteolytic ferment which is most active in acid solutions. Lymphocytes and lymphatic tissue

also contain a fat-splitting ferment which is said to be absent from other forms of leukocytes.

Leukocytosis and Leukopenia

The number of leukocytes in the peripheral blood ordinarily varies from 6,000 to 10,000 per cubic millimeter. When the number is increased, it is called a leukocytosis; when diminished, a leukopenia.

Leukocytoses are distinguished according to the type of cell that is most increased beyond the normal. Most common are the neutrophilic leukocytoses, less common the eosinophilic leukocytoses and the lymphocytoses. At times there is a percentage but not an absolute increase in a certain type of cell, owing to a reduction in the number of other forms.

Physiological Leukocytoses

The number of leukocytes may be moderately increased under a variety of physiological conditions; such as after meals, during the later stages of pregnancy, shortly after birth, after very severe exercise, and after thorough chilling. The leukocytosis of chilling appears to be local in character and to be caused by the marked constriction of the peripheral vessels with slowing of the blood stream. This causes the white cells to accumulate in the cutaneous or subcutaneous vessels.

Digestion Leukocytosis.—Considerable interest is attached to the so-called digestion leukocytosis. This is most marked when an individual, after fasting, eats a meal containing large quantities of protein. Under these conditions the number of leukocytes in the peripheral blood may be increased by about one-third, the increase being particularly marked in the neutrophilic cells. The cause of this leukocytosis is not known, but the increase in neutrophils may possibly bear some relation to the fact that they contain the largest amounts of proteolytic ferment that is active in slightly alkaline media.

Pathological Leukocytoses

(*a*) *Neutrophilic Leukocytoses*

The most important type of neutrophilic leukocytosis is that which occurs in certain infectious diseases; particularly, pneumonia, abscesses, tonsillitis, scarlet fever, and erysipelas. In these conditions leukocyte counts from 15,000 to 20,000 are common and counts of 50,000 or more may occur. The predominant increase is in the neutrophilic cells. The occurrence and the degree of infectious leukocytoses depend upon a variety of factors.

Factors Governing Leukocytoses.—(1) Type of infecting organ-

ism. Infectious cocci are more frequent causes of leukocytosis than are the typhoid bacillus, the colon bacillus or the tubercle bacillus.

(2) Localization of the process. Localized abscesses even when produced by the typhoid or colon bacilli may increase the number of leukocytes, whereas generalized infections with cocci (as in malignant endocarditis) may fail to do so. In tuberculous meningitis a leukocytosis is the rule, whereas it is usually absent in other tuberculous infections.

(3) The reaction of the patient. In a general way the leukocytic reactions are analogous to the febrile reactions that occur in infectious processes. A severe infection with a marked reaction on the part of the patient tends in general to be associated with a high leukocytosis. A mild infection or a failure on the part of the patient to react against a severe infection may each be the cause of low or absent leukocytosis in conditions where increased counts are the rule.

The leukocytosis which follows acute hemorrhage is probably due to the increased activity of the bone marrow that follows a loss of blood.

(*b*) *Eosinophilic Leukocytoses*

Eosinophilias have been observed in a great variety of clinical conditions, among which are infections with parasitic worms, asthma and certain skin conditions (urticaria, pemphigus, dermatitis herpetiformis, etc.)

Trichiniasis.—In trichiniasis the percentage of eosinophils in the blood

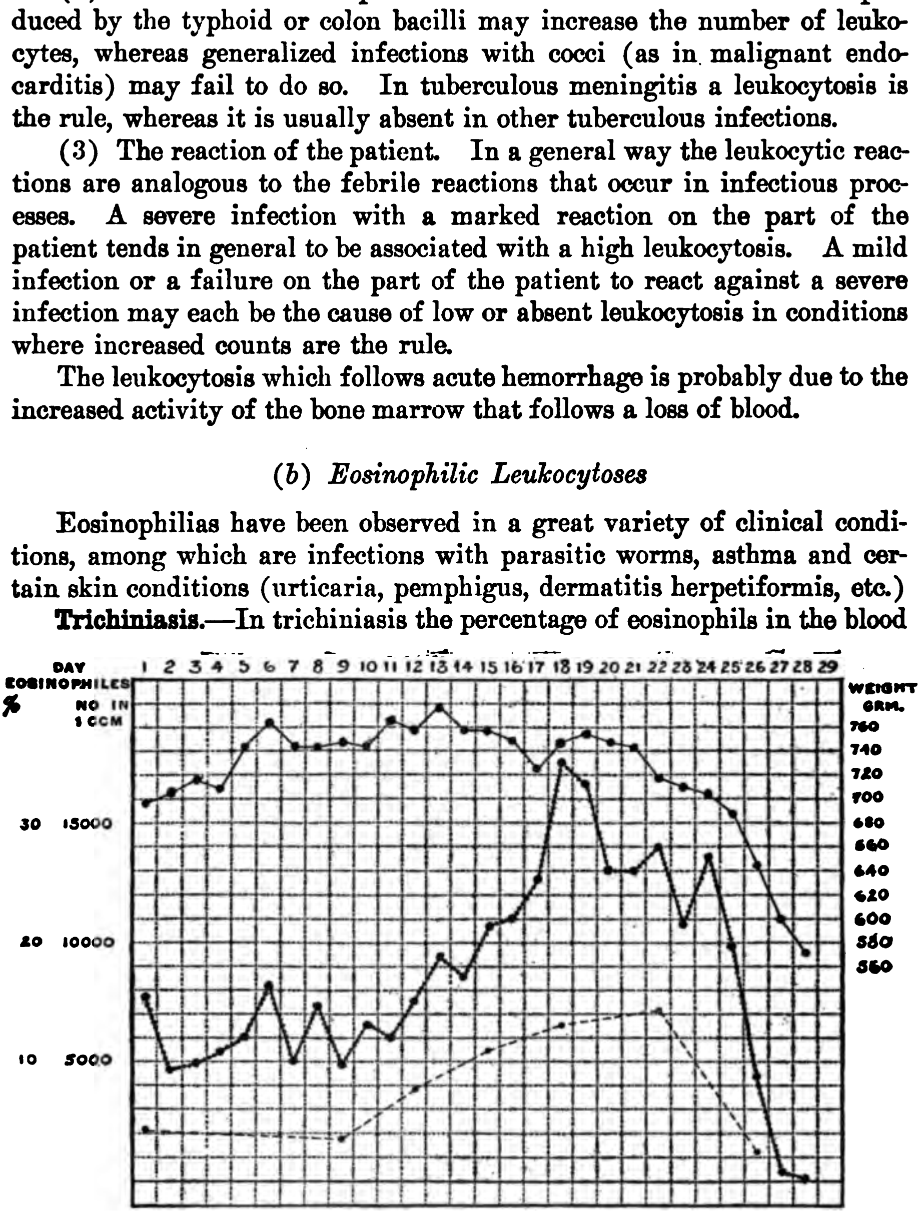

Fig. 125.—Experimental Eosinophilia Produced by Infecting Guinea-pigs with a Moderate Number of the Parasite. The Upper Curve Represents the Weight of the Animal, the Middle Curve the Percentage of Eosinophils, and the Lower Curve the Number of Eosinophils per c.mm. of Blood. Note that the Rise Occurred About the Tenth Day and that There Was a Fall Before the Death of the Animal. (From Opie, Am. Jour. Med. Sci.).

may reach 65 per cent, with a corresponding increase in the total number of leukocytes. Opie has shown that eosinophilia may be produced in guinea-pigs by infecting them experimentally with trichinae. This experimental eosinophilia appears about one week after the infection, reaches its height about the end of the third week and falls below the normal before death. If the animals are infected with an overwhelming dose the number of eosinophils in the blood may be diminished from the start. The

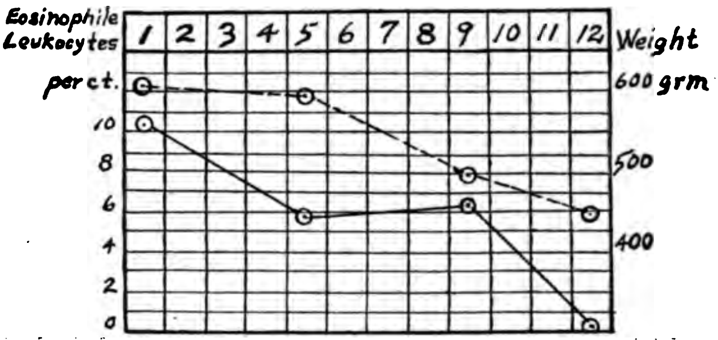

Fig. 126.—Effect Upon Eosinophils of an Overwhelming Infection of a Guinea-pig with Trichinae. Upper Line Represents the Body Weight. Lower Line Represents the Percentage of Eosinophils in the Peripheral Blood. Note that the Fall Begins Early and that These Cells Practically Disappear from the Circulating Blood at the Time of Death which Occurred on the Twelfth Day. (Drawn from data of Opie, Amer. Jour. Med. Sci.)

eosinophilia in these animals is associated with local accumulations of these cells in the mesenteric nodes and in the lungs, presumably because embryos have lodged in these localities and have attracted the cells. In man collections of eosinophils have also been observed in the voluntary muscles about the encysted embryos. The bone marrow in experimental infections is usually increased in extent and shows large numbers of mature and immature eosinophilic cells (polynuclears and myelocytes). In very severe infections, on the other hand, the eosinophilic cells in the bone marrow may show evidences of degeneration.

As an Anaphylactic Phenomenon.—The eosinophilia accompanying asthma and certain exudative skin lesions is possibly to be regarded as an anaphylactic phenomenon, for Schlecht and others have shown that eosinophilia may be produced in the guinea-pig and in the dog by repeated injections of foreign proteins. These eosinophilias are associated with local collections of these cells in the lungs (asthma) and in the skin lesions. The local inflammations, which occur when a foreign protein is repeatedly injected into certain animals (Arthur's phenomenon), also contain a large number of these cells. Finally, vernal conjunctivitis, which may be of an anaphylactic character, is characterized by the occurrence of numerous eosinophils in the exudate.

Bacterial Infection and Eosinophilia.—During bacterial infections

the number of eosinophils in the peripheral blood is frequently diminished, but as the fever subsides their number rises and during convalescence there may be a moderate increase. Similar changes have been observed

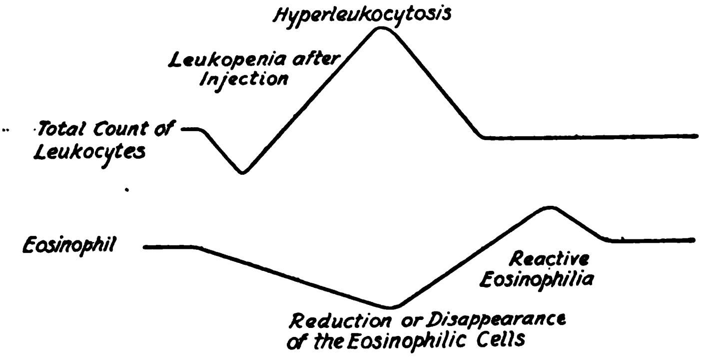

Fig. 127.—Effect of Bacterial Infection Upon the Eosinophils. During the Leukocytosis the Eosinophils Fall and with Recovery There Is a Reactive Eosinophilia. (From Stäubli, "Ergebn. d. inn. Med. u. Kinderheilk.," published by J. Springer, Berlin.)

after the injection of dead cultures into animals. In the region about such injections, eosinophilic cells are rare, either because the bacterial poisons destroy these cells or because they are driven away by negative chemotactic influences.

(c) *Lymphocytosis*

In young infants a lymphocytosis is normal, the percentage of these cells in the blood being 40 per cent or more. During childhood there seems to be a special tendency to the development of lymphocytoses, and increased numbers of lymphocytes have been observed in certain gastro-intestinal disturbances and in cervical lymphadenitis. Whooping-cough is often accompanied by a very striking increase in the number of these cells, particularly in children. In adults a lymphocytosis is occasionally observed during infectious diseases where one ordinarily expects to find an increase in the neutrophils (Cabot). The nature of this form is not clear. Local collections of lymphocytic cells often occur about lesions caused by bacteria that contain lipoid substances (tubercle bacilli, leprosy bacilli). Possibly such collections may be correlated with the observation that lymphocytes possess a special lipolytic ferment.

(d) *Increases in the Large Mononuclears and Transitionals*

An increased number of large mononuclear cells in the peripheral blood has been observed in malaria. The transitionals are increased in Hodgkin's disease, although where a leukocytosis is present this increase may be an absolute one and may not be evident on the differential count

alone. An increase in the number of transitional cells has also been observed occasionally in lymph gland tuberculosis and in typhoid fever. Evans has reported a remarkable case in which the transitionals rose to over 54 per cent for a brief period of time.

Leukopenia

As a rule, a reduction in the total number of leukocytes in the peripheral blood is due to a reduction in the number of neutrophils. As a result of such a reduction there is a high percentage, though not an absolute increase, in the number of other cells and particularly of the lymphocytes. Among febrile diseases, typhoid fever and tuberculosis not infrequently produce such a blood picture.

Pathogenesis of Leukocytoses

An increased number of cells in the circulating blood may be due: (1) to an attraction of such cells out of the tissues in which they are formed or out of collections in the internal organs; or (2) to an increased activity of the tissues that give rise to these cells. The latter condition is responsible for the leukocytoses observed in certain cases of bone tumor, for the leukocytosis following hemorrhage, and for the increased number of leukocytes and their progenitors in leukemia.

Relation to Chemotaxis.—We have seen that bacterial products and various other substances exert a positive chemotactic influence upon the neutrophilic leukocytes, and that an analogous relation exists between certain animal parasites and the eosinophilic leukocytes. It is obvious that when such bacteria or animal parasites gain entrance to the body they will tend to attract certain forms of leukocytes, and in this way a local collection of the attracted cells takes place about the offending particles. Such a local accumulation of cells would tend to diminish their number in the circulating blood. When, however, the chemotactic substances enter the blood they attract cells out of their sites of formation or out of any collections that may be present elsewhere in the body. Under such circumstances, the number of cells in the blood increases, and the increase is due to the particular cells that are attracted by the substance in question.

Increased Activity of Formative Tissues.—As a result of this loss of cells the formative tissues tend to reproduce these cells in greater numbers and an overproduction may take place. Possibly, in addition, the chemotactic or other substances derived from the foreign cells may irritate the formative tissues and thus accelerate their functional activity. In any case, the bone marrow of patients with neutrophilic or eosinophilic leukocytoses usually shows evidences of increased activity. The active marrow may extend beyond its usual limits and the cells in question, as

well as their progenitors, are increased in number and are actively multiplying. Under such circumstances one might anticipate that immature cells would escape into the circulating blood. This is, in fact, the case. The polynuclear cells show an increased percentage of the forms with single or few nuclei, and a diminished percentage of the more highly fragmented forms. Furthermore, small numbers of myelocytes frequently accompany any polynuclear leukocytosis, the myelocytes showing the same granulations as the increased polynuclears.

Pathogensis of Leukopenia

Injury to Formative Tissues.—The leukocytes which wander into the immediate neighborhood of the infecting organisms often succumb to the attacks of the latter, and may be observed in various stages of disintegration. It seems probable that these injurious substances may also enter the blood stream, and thus act not only upon the blood cells but upon the formative tissues. A slight injury to these last may increase their activity; this being, as we have seen, one explanation for the leukocytosis commonly observed during infections. On the other hand, a more serious injury to the bone marrow may diminish the regenerative processes there taking place. Such, apparently, is the explanation for the absence of leukocytosis and for the leukopenia observed in overwhelming infections. If the resistance of the individual is diminished, such a serious damage to the blood-forming tissues is more readily produced. Leukopenia may also be produced by benzol and by exposure to the x-rays, both of which damage the bone marrow. It may be due, furthermore, to an exhaustion or aplasia of the marrow tissue (see Aplastic Anemia).

Collection of Cells in Internal Organs.—Finally, certain forms of leukopenia are due to other causes than a failure on the part of the bone marrow. During anaphylactic shock in the dog, for example, the polynuclear cells practically disappear from the circulating blood. In this case the disappearance seems to be due to a collection of these cells in the internal organs (lungs).

Leukemia and Allied Conditions

General Considerations

By leukemia we mean a diffuse, unrestrained growth of the tissues that give rise to the white blood cells. However important from the clinical standpoint may be the appearance of the blood, the essential change in this disease lies in the hyperplastic or tumorlike (sarcoid) alterations which are found in the blood-forming tissues. As a rule, these are associated with quantitative and qualitative alterations in the blood picture, owing to the entrance of numerous ripe and unripe leukocytes into the

circulation; but the blood picture is not an essential feature of the disease, and to those rare cases in which leukemic changes in the blood-forming tissues have been associated with little or no change in the blood itself the name of aleukemic leukemia has been given.

Two Groups: Myeloid and Lymphatic.—The leukemias are divided into two main groups, the myeloid and the lymphatic. In the former, the myeloid tissues throughout the body show an abnormal proliferation; in the latter, the lymphatic tissues show a similar change. As a general rule, the two forms of leukemia are mutually exclusive. Only a few mixed forms have been described, and the interpretation of such cases as true mixtures of the two types has been questioned.

Chronic Myeloid Leukemia

The anatomical changes in chronic myeloid leukemia consist essentially in a diffuse hyperplasia of the myeloid tissue in the bone marrow. To this may be added the appearance of myeloid tissue in other organs, and particularly in the liver, the lymph nodes and the spleen. The relation of these latter to the bone marrow changes has been variously interpreted. By some, they are regarded as colonizations or metastases of cells which are carried from the bone marrow, deposited in these new sites, and there take root and grow. By others, the opinion has been advanced that these extramedullary areas of proliferation develop in situ from cells that took part in the formation of white blood cells during fetal life. The latter view is founded in part upon embryological considerations, in part upon the observation that such myeloid masses may be present without any corresponding alteration in the bone marrow.

Myelocytes and Myeloblasts.—Histologically these areas of myeloid tissue are characterized by the prevalence of cells which are the normal progenitors of the polynuclear granular cells; i. e., granular mononuclear cells (myelocytes) and non-granular mononuclear cells (myeloblasts).

Blood Picture.—The blood picture in typical cases of myeloid leukemia is characterized by the large number of cells of myeloid origin that appear in the circulating blood. The total number of leukocytes is usually increased to from 100,000 to 800,000. The differential count usually shows about 50 per cent of the polynuclear granular forms (neutrophils, eosinophils, and basophils), about 40 per cent of their ancestral forms (neutrophilic and eosinophilic myelocytes, myeloblasts, and related forms) and a marked reduction in the percentage of typical lymphocytes. In addition, there is frequently a more or less marked anemia, and nucleated red cells in large numbers may appear in the circulating blood. The changes in the red cell formation are due to mechanical or other effects produced by the exuberant growth of myeloid tissue upon the marrow cells that normally give rise to red corpuscles.

Variations in the Blood Picture.—Remarkable changes in the

blood picture of myeloid leukemia may occur. During treatment with the x-ray or with benzol, both of which destroy myeloblastic cells, the leukocyte count may fall even to the normal, the enlarged spleen may lessen in size, and the anemia may improve. Similar changes sometimes occur either spontaneously or as a sequel to acute infections. As a rule, however, the quantitative change in the blood picture is more striking than the qualitative change, for blood smears may still show an unusual number of immature granular cells. At other times the blood picture becomes practically normal. That such changes represent a remission rather than a cure of the disease is evident, however, from the fact that sooner or later a relapse usually occurs.

Chronic Lymphatic Leukemia

The anatomical changes in chronic lymphatic leukemia consist in a diffuse hyperplasia of the lymphatic tissues throughout the body, and especially in the lymph glands, the spleen and the bone marrow. The overgrowth of bone marrow with lymphatic tissue is believed to originate from areas of lymphatic tissue present in this region. An absolute as well as a relative reduction in the number of granular cells in the circulating blood may result from this cause.

Increase of White Corpuscles.—In lymphatic leukemia the number of white corpuscles in the blood is usually increased to from 40,000 to 500,000 per cubic millimeter. Of these from 85 to 99 per cent are small or medium-sized lymphocytes. As a rule, nucleated red cells are less common in the circulating blood than in the myeloid form of leukemia, but at times they appear in large numbers. They are due to the overgrowth of bone marrow with lymphatic tissue.

Effect of Treatment—Aleukemic Types.—As in the myeloid form of the disease, treatment with the x-ray or with benzol may be followed by a marked reduction in the number of lymphocytes in the blood and even with a return to a normal blood picture. Aleukemic types of the disease which do not depend upon treatment are more common than in myeloid leukemia. In such cases, there may be an enlargement of the lymphatic glands which show the typical anatomical picture of lymphatic leukemia. The total leukocyte count is normal or subnormal, but in many cases there is a relative increase in the lymphocytes of the blood.

Acute Leukemia

Acute leukemia is to be separated from the chronic forms by reason of its rapid course, its peculiar blood picture and its resemblance to an infectious disease.

Acute leukemia is, as a rule, rapidly fatal, the illness lasting from one to nine weeks. In some patients, the high fever and great prostration sug-

gest an acute infectious disease; in others, the marked hemorrhagic tendency suggests a diagnosis of purpura hemorrhagica. Blood examinations usually show a moderate to marked increase in the number of white blood corpuscles, the prevailing cell being a large mononuclear form with few if any granules.

Origin of Mononuclear Cells.—Acute leukemia was formerly regarded as a subvariety of the chronic lymphatic form of the disease, differing from it in its rapid course and in the large size of the prevailing blood cells. More recent work, however, indicates that in many, and perhaps in most, of the cases the large non-granular cells that predominate in the circulating blood belong to the myeloid rather than to the lymphatic type of cells. This view is supported by the following facts: (1) typical granular myelocytes may be found in the peripheral blood; (2) anatomical examination may show an especial involvement of the myeloid tissue; and (3) biological tests indicate that the abnormal cells in the blood are more closely related to the granular cells than to the lymphocytes. Longcope, for example, found that the cells in the acute leukemias which he studied possessed proteolytic ferments similar to those possessed by the neutrophilic polynuclears, and others have shown that, in certain cases, these cells may contain the oxidizing ferment which characterizes neutrophilic cells.

Chloroma

This rare neoplasm is characterized anatomically by its green color, by its origin from periosteum, especially that covering the bones of the face, and by an altered blood picture. The latter is similar to or identical with the blood picture of leukemia. Although the number of leukocytes may at times be normal, they are often increased, and in nearly all cases the differential count shows the changes that occur in myeloid, in lymphatic, or particularly, in acute leukemia. In view of these blood findings the view is generally accepted that chloroma is essentially related to leukemia, but that for some reason a tumor is formed which has a structure similar to that of the blood-forming tissues.

Etiology of Leukemia

Despite the large amount of attention that has been paid to this subject, the etiology of leukemia is still unsolved. According to one view, it is caused by an infection which produces a peculiar reaction on the part of the blood-forming tissues. According to the other view, it is a malignant disease of these tissues with an escape of neoplastic cells into the circulating blood.

First Hypothesis: A Malignant Disease.—The view that leukemia is essentially a malignant disease is based upon the fact that in this disease

we have an unrestrained growth of certain cells in the body. It differs from an ordinary neoplasm in that it has no local origin but arises from all the tissues belonging to a certain system; i. e., from those which give rise to certain types of white blood corpuscles. Transitions to localized tumors do, however, occur. As we have seen, chloromata are usually associated with a leukemic blood picture. A less intimate relationship exists between leukemias and the so-called myelomata. The latter are multiple, circumscribed tumors of the bone marrow which invade and destroy the neighboring bone. Histologically, myelomata may be made up of myelocytes, of myeloblasts, of lymphocytes, of plasma cells, or of erythroblastic tissue. The blood picture is not characteristic. Myelomata differ from the aleukemic leukemias in that the new growing tissue is circumscribed and not generalized. In an analogous relation to lymphatic leukemia stand the so-called lymphosarcomata. These show an aggressive infiltrative growth of lymphatic cells, but the process does not involve all of the lymphatic tissues equally. Blood changes may be absent. It is evident, therefore, that we have various transitions between typical leukemia and circumscribed, though multiple, tumor masses, which are composed of similar cells and which may or may not be accompanied by leukemic changes in the blood. If these tumor masses are to be regarded as malignant neoplasms in the narrower sense of the word, then leukemia must also belong to the same category, for no sharp line of separation can be drawn. If, on the other hand, the leukemias are essentially infectious processes, then it seems probable that some, if not all, of these tumorlike new growths are likewise of an infectious character.

Second Hypothesis: An Infectious Disease.—The infectious theory of leukemia is supported by the fact that the acute type of the disease usually runs a course strongly suggesting an acute infection, with high fever, prostration, and a hemorrhagic tendency. Various pathogenic microörganisms have been cultivated from the blood or tissues of such patients and the blood changes of acute leukemia have been found in patients dying of miliary tuberculosis. It is evident, therefore, that if acute leukemia is due to an infection, either the causative organism has not been found or the disease represents an unusual and abnormal reaction on the part of the bone marrow, which may be induced by a variety of microörganisms. The view that leukemia is due to an infection has been strongly supported by the experiments of Ellerman and Bang, who succeeded in transmitting chicken leukemia to normal fowls. They found, furthermore, that such transmission could be accomplished even though all cells were removed by passages through a fine filter. These authors believe, therefore, that chicken leukemia is due to a filtrable virus. Most interesting is their observation that some of the animals inoculated developed the myeloid form of the disease while others developed the lymphatic form.

Relation of Malignant Tumors to Infections.—Perhaps one

should not be too insistent in separating tumors from infections, for it is possible that tumors result either from infections directly or from the irritation produced by infections. Peyton Rous has succeeded in transmitting a sarcomalike tumor from one chicken to another by means of cell free filtrates. Up to the present, however, attempts to transmit other tumors in this way have failed.

Hodgkin's Disease

An enlargement of lymphatic glands in various parts of the body, often associated with an enlargement of the spleen, may occur in a variety of conditions. Among these are the leukemias, generalized tuberculosis of the lymphatic system, and other infectious processes. Anatomical studies by Dorothy Reed and by Longcope have shown, however, that these may be distinguished from a well-defined type of general glandular enlargement to which the name of Hodgkin's disease may properly be applied.

A Systemic Lymphatic Disease.—Hodgkin's disease (lymphogranulomatosis, malignant lymphoma) is a systemic disease of the lymphatic apparatus. The enlarged glands contain lymphocytes, fibroblasts, leukocytes and peculiar giant cells in irregular arrangement. Not infrequently an unusual number of eosinophils are also present. These cellular areas may be separated by areas of necrotic or fibrous tissue.

Blood Picture in Hodgkin's Disease.—The blood picture in Hodgkin's disease is more or less characteristic. According to Bunting, two types must be distinguished: those with a normal and those with an increased leukocyte count. The latter is due to an increase in the neutrophilic cells and it occurs particularly in patients who have had the disease for a year or more. When the number of leukocytes is normal, the transitionals are increased both absolutely and relatively (8 to 15 per cent); when the number of leukocytes is increased, the percentage of transitionals may be normal, but their absolute number is increased. In all cases there is an increased number of blood platelets.

Nature of Disease Obscure.—The nature of Hodgkin's disease is still under discussion. The gross appearance of the glandular masses and their tendency to invade neighboring structures suggest a malignant process. On the other hand, their histological picture suggests a chronic inflammation (lymphogranulomatosis).

Bacteria Isolated from Enlarged Glands.—In recent years a number of investigators have isolated bacteria from the enlarged glands of patients suffering from Hodgkin's disease. Particularly characteristic are the diphtheroid bacilli which have been isolated, among others, by Bunting and Yates. These investigators have also succeeded in producing a disease similar to Hodgkin's by injecting pure cultures of their bacilli into monkeys. The finding of similar organisms in a variety of other clinical conditions, and the question as to the identity of the various

diphtheroid bacilli isolated from cases of Hodgkin's disease, indicate, however, that further study is required before a final decision as to the etiological relationship of these organisms to the disease is established.

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Chapter XII

The Glands of Internal Secretion

The Chemical Regulation of Body Functions

General Considerations

Up to the final quarter of the past century, the attention of physiologists was directed almost entirely toward the nervous control of the various functions of the body. The activities of voluntary muscle, of smooth muscle and of glandular organs could be influenced by stimulating the proper nerves, and this appeared to be the most important, if not the sole, means by which the body controlled and correlated the functions of its component parts. It is true that in 1849 Berthold had shown that the body changes which follow the castration of young cockerels could be prevented by implanting the testicles at some distant part of the body, and that birds operated upon in this manner developed the vocal powers, the desire for combat, the comb and the sexual instincts of normal cocks. This decisive demonstration of a chemical control of development by the sex glands made little impression at the time, however, and the view held sway that the chemical processes of the body consisted solely in a building up and a breaking down of various tissues, in absorption, combustion, excretion and similar processes.

Hormones.—At the present time, however, we recognize that the body functions are regulated not alone by nervous influences, but also by chemical substances that pass from the tissues into the blood stream. We have seen, for example, that carbon dioxid and other waste products of an acid character exert a preponderating influence upon the activities of the respiratory center and thus upon the respiratory movements, that pancreatic tissue, even when separated from its nerve supply, exercises a profound effect upon carbohydrate metabolism, and that pancreatic juice is secreted after the injection of secretin, a substance that can be

prepared by the action of acids or soaps upon the duodenal mucosa. To such substances that are derived from one organ and that influence another after passage into the blood stream, Starling has given the name of chemical messengers or hormones.

The Ductless Glands

With the discovery that certain glands possess ducts and that characteristic secretions escape through these ducts, the functions of these glands seemed well on the way to solution. But the function of certain other glandlike organs which lacked secretory ducts remained a riddle. Among these latter are the thyroid, the parathyroids, the thymus, the hypophysis, the epiphysis and the adrenals. To Brown-Séquard belongs the credit for having impressed the medical world with the view that all glandular organs, be they with or without ducts, may give off to the blood certain substances that are necessary for the welfare of the body as a whole. The essential correctness of his conception is now generally recognized, and the glands that possess such functions are called the glands of internal secretion. These include not only the ductless glands just enumerated, but certain others which elaborate both an external secretion that escapes through the duct and an internal secretion that enters the blood. Among the glands that possess this double function may be mentioned the pancreas, the liver, the duodenal mucosa and the sex glands.

Evidences of Internal Secretion

Direct and conclusive proof that a particular gland supplies an internal secretion to the body is furnished, if peculiar, physiologically active substances can be demonstrated in the blood or lymph that leaves the gland in question. Proof of this character has been furnished only for one gland of internal secretion, the adrenal. It is evident, however, that a failure to find an active substance in the blood that leaves a gland does not demonstrate the absence of an internal secretion; for the secretion poured out may be greatly diluted by the large quantity of blood and of lymph that comes from the gland, and may thus escape detection by any available method.

Effects of Excision and Implantation.—Next in order of value as evidence of internal secretion is the observation that the excision of the gland produces characteristic changes in the vital processes. If to this be added the observation that such changes may be more or less prevented or neutralized by implantation of the gland elsewhere in the body or by the administration of glandular preparations, then the evidence in favor of an internal secretion may also be regarded as conclusive. Demonstrations of this type have been furnished for the internal secre-

tion of the pancreas, the thyroid, the parathyroids, the hypophysis, the adrenals and the sex glands

The Administration of Glandular Extracts.—Finally comes the study of the physiological effect produced by the administration by mouth or by injections of glandular extracts and of other preparations derived from the glands. The demonstration of physiologically active principles in a gland of internal secretion suggests that similar substances may pass into the circulation under normal or pathological conditions, and this possibility is strengthened if, under pathological conditions of supposed hyperfunction, the symptoms correspond to those produced by the administration of glandular substance. Such is the case, for example, in Graves' disease and it is possibly also the case in the diabetes insipidus that sometimes accompanies disease of the pituitary gland.

Types of Glandular Disturbance

Hypofunction.—Diminished function of a gland of internal secretion is suggested, when the anatomical changes present are those of aplasia or destruction and when the symptoms correspond with those that follow the surgical extirpation of a part or of the whole of the gland in question. If, in addition, the symptoms are relieved by the administration of glandular products or by the successful transplantation of the gland in question, the evidence of diminished or absent function is conclusive.

Hyperfunction.—An excessive or hyperfunction of a gland of internal secretion is suggested when the clinical symptoms of a disease resemble those produced by the administration of the gland in question, and when, furthermore, the anatomical study of the gland shows hyperplastic or other changes, indicative of increased functional activity of its cells. Further evidence of hyperfunction is furnished by the results of operative removal of a part of the diseased structure. If, after such removal, normal conditions become reëstablished the evidence of hyperfunction is conclusive.

Aberrant Types.—There remain for discussion a not inconsiderable number of clinical conditions which are evidently referable to pathological disturbances of the glands of internal secretion but which do not fall clearly either into the group of hyperfunctions or into the group of hypofunctions. The cause of these aberrant types of disease is not altogether clear. We know that certain glands of internal secretion, such as the hypophysis and the adrenals, possess a complex structure and that the different parts show different physiological properties. It is possible also that, where the structure is of a homogenous character, the gland may secrete more than one physiologically active substance. In either case, it is conceivable that under pathological conditions one element in the secretion may be increased, whereas another is normal or diminished.

In such cases, the clinical disease may represent a mixture of the effects produced by variations in the component elements of the glandular activity. Possibly also the deviations from the typical pictures of hyperfunction and hypofunction are due to some peculiar reaction on the part of the individual patient. It is possible, finally, that variations from the characteristic pictures may be due not only to changes in the quantity of the secretion, but also to changes in its quality. Indubitable proof of such a *dysfunction* is not easily furnished, but it affords a ready and convenient explanation for many aberrant types of internal glandular disease.

Disturbances of the Thyroid Gland

Hypothyroidism

The condition, now recognized as hypothyroidism of adults, was first described in 1873 by Sir William Gull. Five years later it was given the name of myxedema by Ord, who found a mucinlike material in the subcutaneous tissue of a patient coming to autopsy. The relation of myxedema to the thyroid gland did not become clear, however, until the surgeons, Reverdin of Geneva and Kocher of Berne, had described a similar condition which followed the complete extirpation of goiterous thyroid glands from their patients. The suggestion that both diseases were due to a lack of thyroid secretion called forth a multitude of studies, both as to the effect of thyroid extirpation upon animals, and the effect of thyroid administration and transplantation on those suffering from these diseases. As a result of these studies it became evident that a diminished or absent thyroid secretion produces a definite clinical picture.

Myxedema of Adults

We have seen that the name myxedema was given to this disease on account of the peculiar swellings observed in the subcutaneous and other tissues. Although such swellings suggest at first an ordinary edema, they differ from this in that they do not pit on pressure and that on anatomical examination they contain a mucinlike material. In pronounced cases of the disease, such swellings are more or less general over the body. They are, however, particularly marked about the cheeks, the nose and the eyelids. The immobility which they cause gives to the face a peculiar, expressionless appearance. Swellings are also common in the neck, above the clavicles, and on the backs of the hands and feet. Such swellings are caused in part by the mucinlike material just mentioned, in part they are due to an increase in the connective tissues.

Thickenings in Mucous Membrane.—Similar thickenings may appear

Fig. 128.—True Myxedema Before and After Thyroid Treatment. Note the Baldness. (From Hertoghe, by permission of the Editor of the Practitioner.)

in the mucous membranes. The tongue becomes enlarged, the voice becomes hoarse by reason of an involvement of the vocal cords, mouth breathing may result from a thickening of the palate and pharynx, and deafness may be due to involvement of the middle ear or of the eustachian tubes. The joint and muscle pains so common in this class of patients are believed to be caused by myxedematous infiltrations of the muscles and the periarticular tissues.

Fig. 129.—Same Patient As in Previous Figure, Before and After Treatment. (From Hertoghe, by permission of the Editor of the Practitioner.)

Tegumental Changes.—In addition to these characteristic swellings, patients suffering from myxedema show various changes in their tegumental structures. The skin is dry and has a peculiar sallow color, the nails are brittle, the hair is both dry and brittle and tends to fall, while the teeth decay and are lost.

Depression of Bodily Functions.—Finally, a depression of various body functions takes place. The basal metabolism is diminished and the patients avoid exercise. The weight is usually increased. The alimentary tolerance for sugar is often greater than nor mal. The temperature tends to be somewhat subnormal and the heart action is slow. Menstruation usually ceases. Characteristic mental changes appear, the most common and striking being apathy and somnolence.

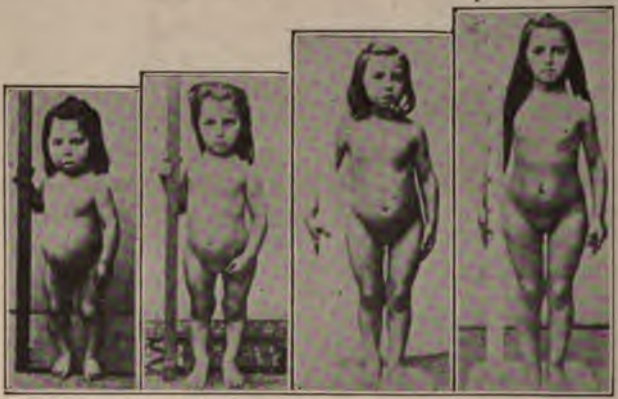
Fig. 130.—True Myxedema Before and After Treatment. Note the Loss of Eyebrows and the Coarse Features. (From Hertoghe, by permission of the Editor of the Practitioner.)

Mild Types of Hypothyroidism

In addition to the outspoken cases of myxedema with characteristic swellings, a variety of milder and less characteristic forms have been described. Thus Marchiafava described a form of thyroid insufficiency which was characterized by apathy and somnolence. In other cases, joint pains, defective menstruation, hoarse voice, deafness, and severe constipation have been attributed to this cause. Finally, von Noorden believes that certain forms of obesity are due to a partial thyroid insufficiency (see Obesity). In all such cases, the assumption that a patient is suffering from a mild type of hypothyroidism is based in part upon a similarity of the symptoms observed to those of typical myxedema, and in part upon the beneficial results which have followed the administration of thyroid preparations.

Sporadic Cretinism

When hypothyroidism occurs in early life (sporadic cretinism) the effects are particularly striking, for the reason that the thyroid secretion is an essential factor in the normal development of mind and body. In sporadic cretins the bony development is incomplete. The formation of the centers of ossification is delayed and the epiphyses unite with the long bones either late or in severe cases not at all. The lack of growth in the long bones leads to a dwarf stature, the lack of growth of the facial bones causes the face to be small relative to the size of the cranium, while the lack of development of the sphenoid gives a sunken appearance to the base of the nose. The fontanels do not close until late in life and dentition is delayed.



a b c d

Fig. 131.—True Infantile Myxedema (Sporadic Cretinism). (a) Before Treatment. The Child Is Eight Years Old. Height Is 34 in. Note the Enlarged Abdomen and Deformities of the Bones of the Lower Limbs; (b) After One Year of Treatment; (c) After Two Years of Treatment, and (d) After Five Years of Treatment. (From Hertoghe, by permission of the Editor of the Practitioner.)

Mental Development.—The mental development of cretins is likewise imperfect and in pronounced cases the individual never attains a mental development beyond that of late infancy.

Resemblance to Myxedema.—Changes in nutrition and in the tegumental structures, as well as mucinous deposits, resemble those which occur in myxedema. The basal metabolism is definitely diminished. The abdomen is often distended.

Retarded Development in Mild Types.—Milder types of hypothyroidism in infants and children retard the mental, bodily and sexual development. The patients are stupid, undersized, and sexually infantile.

Relation of the Thyroid to Sporadic Cretinism and Myxedema

That myxedema and sporadic cretinism are due wholly or in large part to a deficient secretion of the thyroid gland may be regarded as definitely established. The typical complex of myxedema has followed

Fig. 132.—Photograph of Cretin Lamb About One Year Old and of a Normal Lamb of Eleven Months. (From Simpson, Quart. Jour. Exp. Physiol., published by Charles Griffin & Co., London.)

the operative removal of the gland in man. The removal of the thyroid from very young animals has led to changes similar to those of sporadic cretinism. The long bones remain short, psychic apathy may occur (sheep), the hair differs from that of normal animals, and sexual development is delayed or absent.

Effect of Use of Thyroid Substances.—The administration of thyroid substance to myxedematous patients causes striking changes. The swellings disappear, the skin becomes warm and soft, the metabolism is accelerated and the mental apathy and stupor disappear. The administration of thyroid substance to sporadic cretins causes, in addition, a development of the mind, the body and the sexual functions. The transplantation of thyroid tissue derived from other individuals into various parts of the body has been followed by similar changes, but in most, if not in all, instances the tissue so transplanted has ultimately degenerated

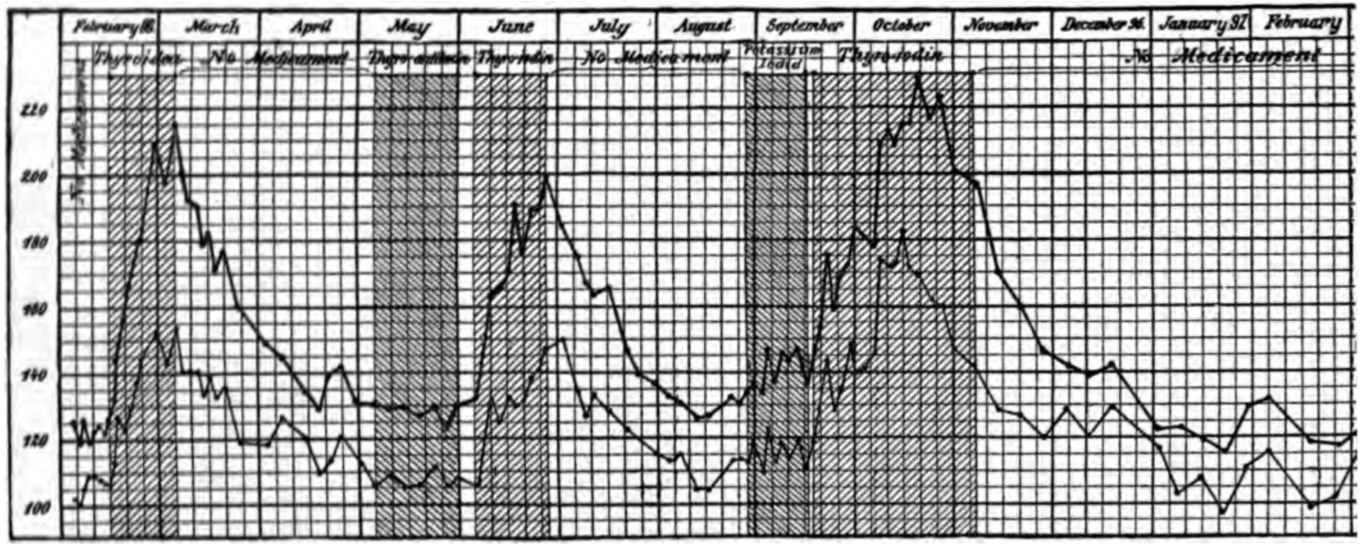


Fig. 133.—The Effect of Thyroid Medication Upon the Gaseous Metabolism of a Sporadic Cretin. Upper Curve Oxygen Consumption and Lower Curve Carbon Dioxid Elimination in c.c. per Minute. Note that Thyreo-antitoxin Produced No Effect and Potassium Iodid But Slight Effect. Thyroid Preparations, on the Other Hand, Caused a Marked Acceleration in the Metabolism. (After Magnus-Levy, Ztschr. f. klin. Med., published by A. Hirschwald, Berlin.)

and the symptoms have returned, so that the hope for a permanent cure by surgical means has not been realized.

RESTORATION OFTEN INCOMPLETE.—In many instances patients have been restored to a normal or nearly normal condition by the administration of thyroid substance, and have relapsed into their original state when the administration of thyroid was discontinued. At times, however, the patients have been improved by thyroid administration only to a certain point. If the administration of thyroid substance were pushed beyond this point toxic symptoms of hyperthyroidism have appeared even when certain symptoms of myxedema were still present. In sporadic cretinism, also, the administration of thyroid substance, while causing a marked improvement, has often failed to restore the individual to a perfectly normal condition. The reason for such partial failures of thyroid medication is not altogether clear. Possibly, as Falta suggests, the failures may be due to various complications, such as involvement of other glands of internal secretion and degenerations of the heart muscle or of other tissues. Possibly, also, the thyroid medication used does not provide a perfect substitution therapy or possibly the original disease is due not to hypothyroidism alone but also to some perversion of the secretion (dysthyroidism).

Hyperthyroidism

Experimental Hyperthyroidism

For the production of experimental hyperthyroidism two general methods have been employed. The first of these consists in the administration of thyroid preparations, the second in increasing the functional activity of the thyroid gland.

(1) *Effects of Thyroid Administration*

The remarkable improvements that have followed the administrations of thyroid preparations to myxedematous patients and to sporadic cretins, naturally led to studies of the effect of these preparations on other diseases and on normal animals and men. Toxic symptoms can be induced in most and probably in all animals by thyroid feeding. As Carlson and his associates have shown, however, the resistance to such feeding varies widely in the different species. Carnivora are relatively resistant, herbivora less so, while man appears to be the most susceptible to thyroid feeding. The most constant symptoms observed are loss of body weight, gastro-enteritis, and diarrhea. As a rule, animals develop neither a rapid heart rate, increased nervousness, nor exophthalmos.

Effect on Man.—Thyroid substance has been administered to man mainly for therapeutic purposes. During such administration toxic

symptoms not infrequently appear. These consist of loss of weight, feelings of warmth and sweating, tachycardia, trembling, restlessness, insomnia, and gastro-intestinal disturbances. In a remarkable case reported by Notthafft, the patient, who had been gaining weight, took nearly a thousand thyroid tablets during the course of five weeks. In addition to most of the above symptoms he showed rapid respirations, slight rise of temperature, glycosuria, and bilateral exophthalmos. The susceptibility to thyroid medication certainly varies considerably in different individuals, and persons with thyroid disease, whether myxedema or Graves' disease, often seem peculiarly prone to develop toxic symptoms. Even in normal individuals, however, large doses often produce tachycardia and losses of weight.

Effect on Metabolism.—The effect of thyroid medication upon the metabolism of normal and of pathological individuals has been repeatedly studied, but here again considerable variations have been noted among different subjects. In some cases at least, the administration of thyroid preparations has increased the general rate of metabolism and the elimination of nitrogen (see Metabolism).

(2) *Thyroid Stimulation*

The administration of iodin preparations to patients with thyroid disease is occasionally followed by a group of symptoms that are similar in character to those produced by the administration of thyroid substance itself. Among these are tachycardia, tremor, increased nervousness and loss of weight. These effects may be produced in susceptible individuals by relatively small doses. Apparently in such cases the iodids cause the liberation of an excessive amount of thyroid secretion. It need hardly be stated that such effects are rarely if ever produced in normal individuals.

Stimulation of Nerves.—Cannon and his associates have shown that it is also possible to produce the symptoms of hyperthyroidism experimentally in cats by anastomosing the central end of the cut phrenic nerve with the peripheral end of the cut cervical sympathetic. After union has taken place, the rhythmical stimuli, which normally pass down the phrenic nerve to the diaphragm during each respiration, are carried to and act upon the thyroid gland. Following this operation the animals become unusually excitable, develop tachycardia and diarrhea, and have a high basal metabolism which may indeed exceed twice the normal. The effects obtained by this procedure correspond to the symptoms observed when thyroid substance is given in excess to susceptible individuals, and they are, as we shall see, very similar to those present in exophthalmic goiter.

Exophthalmic Goiter

Manifestations

In addition to the goiter, the characteristic manifestations of this disease consist of: (a) metabolic changes; (b) ocular changes; (c) cardiovascular changes; and (d) nervous changes.

(a) Metabolism.—In typical exophthalmic goiter the rate of body metabolism is always increased. While this increase is enhanced by the nervousness and by the restless muscular activity of these patients, it remains higher than normal even when these extraneous influences are, so far as possible, eliminated. The basal metabolism in Graves' disease is frequently from 50 to 80 per cent above the normal; and there is probably no other condition, aside from the experimental hyperthyroidism produced by Cannon, in which the basal metabolism equals that seen in severe cases of exophthalmic goiter. Furthermore, the increase is roughly proportional to the severity of the clinical manifestations. To this increased rate of metabolism, as well as to the muscular activity so commonly present, is due the loss of weight that may occur even when the patient is eating well, the tendency to a slight elevation of body temperature, and the warm and moist skin that serves to increase the elimination of heat from the body.

Nitrogenous Metabolism; Glycosuria.—Not only is the total metabolism increased but there is frequently, in addition, an increase in the nitrogenous metabolism which renders the maintenance of nitrogenous equilibrium difficult. Patients with exophthalmic goiter often show also an unusual tendency to alimentary glycosuria, despite the fact that excessive quantities of material are being consumed in the body. Cramer and Krause observed that the administration of thyroid to animals lessened the amount of glycogen in the liver. It is possible, therefore, that the alimentary glycosuria of Graves' disease is due to some failure on the part of the liver to perform its normal glycogenic function when excessive quantities of sugar are taken by mouth.

(b) Ocular Signs.—The protrusion of the eyeballs, to which symptom exophthalmic goiter owes a part of its name, may develop gradually or it may appear quite suddenly. Occasionally it varies markedly within short periods of time. It is possible that these variations may result, as some have held, from vascular changes in the vessels lying in the orbit. It is more probable, however, that the exophthalmos is due to a spasm of the smooth muscle fibers, described by Müller and by Landström. These fibers extend about the eyeball and are attached to the lids and the anterior orbital fascia. Their contraction tends to draw back the lids and to protrude the eyeball. This smooth muscle is innervated by the

cervical sympathetic nerve, and stimulation of this nerve produces, among other effects, a widening of the palpebral fissure and a protrusion of the eyeball. Extirpation of the superior cervical sympathetic ganglion from patients with exophthalmic goiter has frequently been followed by a noteworthy reduction of the exophthalmos, a fact which supports the view that the protrusion of the eye is due to an unusual activity of the smooth muscle fibers in the orbit.

Fig. 134.—Exophthalmic Goiter. Note the Moderate and Uniform Enlargement of the Thyroid Gland, the Emaciation, and the Protrusion of the Eyeball with Retraction of the Upper Lid.

Persistence of Protrusion.—After exophthalmos has persisted for some time, there appears to be a deposit of fat in the posterior orbital tissues which tends to fix the eyeball in its new position. For this reason, it not infrequently happens that patients, who have recovered from other symptoms of exophthalmic goiter, continue to show a prominence of the eyes.

Action of Other Orbital Muscles.—The other ocular manifestations of this disease may also be explained by assuming a spasm of the smooth muscle fibers in the orbit, which tends to retract the lids and to interfere with the movements of the ocular globe. Possibly, also, the failure of the upper lid to follow the movement of the eyeball as the patient watches an object move from above downward (Graefe's sign), the widened palpebral tissure (Dalrymple) and the retraction of the upper lid when the patient looks intently at an object (Kocher), are all due to a spasm of the levator of the upper eyelid. The imperfect convergence of the eyes when an object is held close to the face (Moebius) may be due to a weakness of the internal recti.

(c) Cardiovascular Symptoms.—An almost constant manifestation of exophthalmic goiter is tachycardia. This is believed to be due to a stimulation of the cardiac accelerator nerves. Palpitation and accidental murmurs are also common. In addition, and especially in chronic cases, there may be evidence of changes in the heart muscle, such as dilatation and cardiac insufficiency, extrasystoles and auricular fibrillation.

The blood pressure may be normal, elevated or reduced. The arteries often show excessive pulsations. The warm skin is due to an increased blood flow to the surface. By this means the body eliminates the extra heat produced by the increased rate of metabolism.

THYROID GLAND UNUSUALLY VASCULAR.—The thyroid gland in Graves' disease is unusually vascular and its vessels bleed profusely at operation. The thrills and murmurs observed about the glands are due to the rapid blood flow in this organ. The cause of the systolic murmurs so frequently heard over the heart is not known.

(d) Nervous Symptoms.—Patients suffering from exophthalmic goiter are, as a rule, nervous and emotional. They speak and move quickly. Tremors of the hands and tongue are common. Occasionally a definite psychosis develops. It is probable that nervous influences play a part in causing the disease. Nervousness is also a result of thyroid disease, for increased nervousness has been produced by thyroid administration to susceptible individuals, and the nervousness of patients suffering from Graves' disease often abates after partial thyroidectomy. In this disease, therefore, a vicious circle tends to become established, for the thyroid disease increases the nervousness, while the latter probably stimulates the thyroid to increased activity.

(e) Other Manifestations.—Among the other disturbances in exophthalmic goiter are muscular weakness, rapid and superficial respirations, increase of mononuclear cells in the blood, diarrhea, and pigmentations.

Pathogenesis of Exophthalmic Goiter

Many facts favor the view that exophthalmic goiter is due, at least in part, to a hyperfunction of the thyroid gland. When thyroid substance is administered to susceptible individuals, it produces tremors, increased nervousness, rapid metabolism, loss of weight, sweating and tachycardia, all of which are analogous to the symptoms present in the disease. As a rule, exophthalmos does not follow the administration of thyroid substance either to man or animals, but in a few instances it has been observed (Notthafft). While the susceptibility of different individuals to thyroid administration varies considerably, it is a rule that patients with a mild form of exophthalmic goiter are made worse by such administration.

Structure of Gland.—The appearance of the gland in patients suffering from exophthalmic goiter also favors the theory of hyperfunction, for in addition to its increased vascularity the number and size of the epithelial cells are increased. The acini contain but little colloid and are almost filled with hyperplastic and desquamating epithelial cells.

Effect of Partial Thyroidectomy.—Further evidence of increased function is furnished by the results of surgical operation. Immediately

after partial thyroidectomy there is not infrequently an acute exacerbation of symptoms with very rapid pulse, great restlessness and extreme nervousness. These symptoms of acute intoxication are probably due to the action of thyroid secretion that has been liberated during or immediately after the operation. After recovery from the operation, however, the symptoms are usually greatly benefited or even cured.

Excess of Thyroid Secretion in Blood Unproven.—Conclusive demonstration of an excess of thyroid secretion in the blood of patients suffering from exophthalmic goiter has not been furnished. R. Hunt has shown that when small amounts of thyroid substance are fed to mice they acquire a marked increase in their resistance to the poisonous action of acetonitril. By feeding the blood of patients suffering from exophthalmic goiter to mice Hunt was able to increase their resistance to this drug in two of three patients. Carlson and Woelfel, however, failed to confirm this observation in one patient and Carlson's blood did not show the test, even after he had taken sufficient thyroid substance by mouth to produce toxic symptoms.

Contrast with Cachexia thyreopriva.—The view that Graves' disease is due to a thyroid hyperfunction was originally advocated because of the contrast between the clinical manifestations of this disease and those produced by a removal of the gland. A. Kocher has tabulated this contrast in the following form:

Cachexia thyreopriva	Graves' Disease
Absence or atrophy of the thyroid gland	Swelling of the thyroid gland, usually of a diffuse nature. Hypervascularization
Slow, small, regular pulse	Frequent, often tense and at times irregular pulse
Cold skin, without flushings	Irritable vasomotor system
An uninterested, quiet stare without expression of life	Anxious, changing glances, angry expression
Narrow palpebral aperture	Wide palpebral aperture, exophthalmos
Slow digestion and excretion, poor appetite, requiring little food	Abundant excretions, an excessive appetite with increased needs of food
Retarded metabolism	Increased metabolism
Skin is thick, opaque, folded, dry and scaling	Skin is thin, transparent, finely injected and moist
Short, thick fingers with broad ends	Long, slender fingers with pointed ends
Sleepy	Wakeful and disturbed sleep
Slow sensation, apperception and action	Increased sensation, apperception and action
Lack of thoughts, interest and emotion	Flight of ideas, psychic excitation even to hallucination, mania and melancholy
Slow, awkward, muscular movements	Constant activity and haste
Stiffness of the extremities	Tremor and increased mobility of joints

Cachexia thyreopriva	Graves' Disease
Delay in growth of bones, often with deformities. Bones thick and short	Slender skeleton with here and there soft bones
Constant chilliness	Unbearable feeling of heat
Slow, difficult breathing	Superficial breathing with imperfect inspiratory expansion
Increase of weight	Loss of weight
Aged appearance even of young people	Youthful rank development of the body, especially at the onset

Objections to Hypothesis of Hyperfunction.—Many facts have, therefore, been brought forward in support of the view that Graves' disease is caused by hyperfunction of the thyroid gland. Nevertheless, certain observations upon patients are not readily explained on this hypothesis. The various symptoms are not equally developed in all patients. The eye signs may be absent or the cardiac disturbances unusually prominent. In chronic cases with tendency toward recovery the symptoms of Graves' disease often appear to be combined with symptoms of thyroid insufficiency and the same combination may develop after partial thyroidectomy. Whether these variations are due to qualitative changes in the function of the gland (dysthyroidism), to degenerative changes in other parts of the body, to alterations in other internal secretions, or to individual peculiarities on the part of the patient is not certain.

Effect of Enlarged or Overactive Thymus.—In recent years particular attention has also been paid to the part which an enlarged or overactive thymus may play in contributing to the symptom-complex of exophthalmic goiter. As a result of clinical and anatomical studies, A. Kocher estimates that in from 45 to 50 per cent of all patients suffering from Graves' disease there is an enlargement of the thymus gland. It appears, furthermore, that in certain instances the operative results following partial thyroidectomy are improved if the thymus is also excised or if a secondary treatment of the thymus with the x-ray is carried out. Up to the present, however, the evidence indicates that the part played by the thymus in producing the typical picture of exophthalmic goiter is secondary in importance to the part played by the excessive and perhaps perverted thyroid secretion.

It appears probable, therefore, that while the symptoms of exophthalmic goiter are due in the main to a hypersecretion of the thyroid gland, there are not infrequently other changes, either in this secretion itself or in other parts of the body, which alter the fundamental picture of hyperthyroidism.

Etiology of Exophthalmic Goiter

Concerning the cause of the thyroid changes that lead to exophthalmic goiter we know little. Clinicians have frequently pointed out that the

symptoms of this disease occasionally develop after some unusual *excitement or emotion*, and that practically all patients do badly when exposed to exciting influences. The work of Cannon, already referred to, has demonstrated that hyperthyroidism may result from stimulation of the nerves leading to the thyroid gland, and Rabe, Rogers, Fawcell and Beebe showed that stimulation of one cervical sympathetic nerve led to demonstrable changes in the corresponding lobe of the thyroid. There is every reason to believe, therefore, that nervous influences not only predispose to but may actually induce the disease.

We have also pointed out that in certain patients with thyroid disease toxic symptoms develop or become more marked when *iodids* are given. In some cases acute or subacute inflammations of the gland appear to have given rise to the symptoms of hyperthyroidism, but the frequency with which *infectious processes* are responsible for Graves' disease is not settled.

The Active Principle of Thyroid Secretion

Nor are we well informed concerning the active principle in thyroid secretion. It is known that this gland possesses a peculiar affinity for iodin and that the percentage of this element in thyroid substances is often eight to ten times as great as its percentage in other tissues of the body. Furthermore, when the body is subjected to iodin want the thyroid retains its iodin with peculiar tenacity. The occurrence of toxic symptoms, in certain patients suffering from thyroid disease, after the administration of iodids also favors the view that this element has some peculiar relation to thyroid activity. Finally, the activity of thyroid preparations, as tested by Hunt's acetonitril test, runs more or less parallel to their content of iodin; though even iodin free thyroid may show some activity.

An Organic Iodin Compound.—It seems probable, therefore, that the active principle of thyroid secretion is an organic iodin compound. A variety of such compounds have been prepared from thyroid substance, among which are Oswald's iodothyroglobulin and Baumann's iodothyrin. More recently Kendall has prepared a relatively simple, crystalline, iodin-containing compound by subjecting the thyroid substance to hydrolysis with alkaline alcohol, and he has shown that small doses of this preparation give rise to symptoms comparable to those of hyperthyroidism. It may be pointed out, however, that the sole reliable test for an efficient substitute for thyroid substance consists in an ability to counteract the effects of thyroidectomy in animals, or to cause striking improvement in cases of human myxedema and sporadic cretinism. Such an action has been demonstrated for certain protein-iodin compounds isolated from the thyroid (iodothyroglobulin), but up to the present it has not been demonstrated for the simpler iodin derivatives of the gland.

Endemic Cretinism, Endemic Goiter and the Goiter Heart

The etiology of various other diseases of the thyroid gland and their relation to the body as a whole have been much studied, but many points remain obscure.

Endemic Cretinism

That the thyroid gland is diseased or almost absent in those suffering from the endemic type of cretinism is certain, but the relation of this disease to sporadic cretinism is not definitely known. As contrasted with the latter, endemic cretins exhibit myxedematous swellings less frequently and the psychic and bodily development vary greatly. Furthermore, the administration of thyroid substance to endemic cretins is less successful than its administration to those suffering from the sporadic form of the disease. According to some, these differences are not sufficient to separate the two diseases; according to others, endemic cretinism is a general disease and the thyroid changes are but one manifestation of the general disease. The frequency of deaf-mutism in regions where endemic cretinism and endemic goiter prevail has been held to prove that all are due to a common cause.

Endemic Goiter

Endemic goiter, like endemic cretinism, occurs in certain districts and particularly in the mountainous regions of the Alps, the Pyrenees, the Carpathians, the Himalayas and the Andes. It is not restricted to mountainous districts, however, but appears to occur in association with certain geological formations. The cause of endemic goiter has been variously attributed: (1) to the water supply, which may contain an improper mixture of salts or a colloidal poison (Bircher); (2) to nutritional disturbances; or (3) to infections.

Experiments on Trout.—Of interest in this connection are the experiments of Marine, who found that young trout could be made goiterous by feeding them on hog's liver and heart, whereas the goiters could be avoided and cured by feeding the meat from sea fish.

Toxic Symptoms in Goiter.—The functional activity of the thyroid gland cannot be judged from its size. Endemic cretins often show large goiters and goiters are frequently accompanied by no toxic symptoms (simple goiters). Indeed, the administration of thyroid substance or of iodids to patients with simple goiter has not infrequently been followed by a reduction in the size of the tumor and a coincident development of toxic symptoms. Patients who have had a simple goiter for years may eventually develop toxic symptoms (secondary Graves' disease) although no change in the size of the goiter occurs. It is obvious, therefore, that

the storage of material (colloid) in the gland must be distinguished from the liberation of active secretion. The latter alone is capable of inducing toxic manifestations.

The Goiter Heart

Patients suffering from apparently simple goiters are peculiarly liable to cardiac disturbances. These may be caused by pressure of the tumor upon neighboring structures. Compression of the trachea causes an inspiratory dyspnea with unusual fluctuations of the intrathoracic pressure and this, as we have seen (page 42), may be a cause of cardiac disease (goiter heart of Rose). Pressure upon the sympathetic or vagus nerves in the lower neck or upper thorax may also alter the heart action.

Toxic Nature of Most Disturbances.—The majority of cardiac disturbances associated with goiter are probably of a toxic nature. At times the cardiac manifestations resemble those seen in Graves' disease, even though other manifestations of this disease are absent. In such cases, particularly, the toxic nature of the cardiac disturbances seems probable. Furthermore, patients with goiter, whether simple or exophthalmic, not infrequently show evidence of myocardial disturbances, such as dilatation, hypertrophy, and irregularities (extrasystoles and auricular fibrillation). The occasional occurrence of transient auricular fibrillation after partial thyroidectomy also indicates that toxic substances of thyroid origin may disturb the heart rhythm.

Hypothesis of General Intoxication.—While the author agrees with those who hold that the cardiac manifestations associated with goiter arise for the most part from thyroid intoxication, it should be mentioned that certain authors believe that these manifestations are due, not to the goiter directly, but to the general intoxication which is responsible for the changes in the thyroid gland.

The Parathyroids

It was noted by early observers that complete removal of the thyroid gland produced variable effects. While some subjects developed symptoms that closely resembled those of myxedema, others showed acute symptoms of a convulsive character. The latter effects were particularly common in dogs, and it was thought at first that thyroidectomy produced results in carnivora which differed from those produced in herbivora. Further studies, initiated by Gley and by Vassale and Generali, showed, however, that the convulsive seizures observed in certain animals were due, not to a removal of the thyroid gland, but to the removal of the small parathyroid glandules that had been described by Sandström in 1880. The varying results observed after such operations were due to the varying amounts of parathyroid tissue that had been excised with the thyroid.

When, as in some animals, all the parathyroids are intimately connected with the thyroid, excision was often followed by tetany; whereas, when two or more of the parathyroids were at some distance from the thyroid, they readily escaped removal and after operation such animals became myxedematous. Finally, the excision of all the parathyroids with as little thyroid tissue as possible resulted in tetany.

Symptoms of Tetany

Tetany is characterized by an increased irritability of the nervous system, associated with muscular tremors and convulsive seizures that affect particularly the hands and feet. The peripheral nerves show an increased irritability to the galvanic current (Erb) and frequently also a variation from their normal responses to the opening and closing of this circuit. Pressure over a nerve (Trousseau) or mechanical stimulation of a nerve by tapping (Chvostek) may induce muscular contractions or spasms. There is also an increased irritability of the sensory nerves to the electrical current and the same is true of the acoustic nerve.

Experimental Tetany after Parathyroidectomy

The excision of all parathyroids leads to the characteristic nervous manifestations of tetany that have just been described. The effect upon the internal organs has also been studied. While Falta and Kahn found that patients suffering from clinical forms of tetany show a tendency to spasms of the stomach, the ciliary muscles and the blood vessels, as well as to a hypersecretion of sweat, tears, and the digestive juices, Carlson found that in cats and dogs parathyroidectomy tends, if anything, to depress the movements of the gastro-intestinal canal, and Keeton that it lessens the secretion of gastric juice. Hoskins and Wheelan have noted that parathyroid deficiency increases the reactions of the blood vessels to certain drugs (epinephrin, pituitrin and nicotin).

Peripheral Nature of Increased Nervous Irritability.—In tetany the peripheral neuron which extends from the spinal cord to the muscle is altered. Convulsive seizures still occur in the hind extremities even after the spinal cord has been severed. Furthermore, MacCallum and his associates have shown that the electrical irritability of a peripheral nerve is altered in the characteristic manner if an extremity be perfused with blood from a parathyroidectomized animal or with blood from which calcium salts have been removed. This local hypersensitiveness of the nerves disappears if the extremity be again supplied with normal blood. Although the peripheral nature of many nervous manifestations of tetany has been demonstrated, it seems probable that in severe types of the disease the motor cells of the brain may also become affected, thus causing epileptiform seizures.

Metabolism in Experimental Tetany

The metabolism of animals following parathyroidectomy has been repeatedly studied. Various changes in nitrogenous metabolism have been described, and particular attention has been paid to the increased excretion of ammonia which has been observed in certain instances. The relation of this increased ammonia output to the tetanic convulsions has been variously interpreted. Wilson and his coworkers have recently found that acid administration produced a beneficial effect upon parathyroidectomized animals, and it has been suggested that an abnormal accumulation of alkali in the body may be partly responsible for the symptoms of tetany.

Disturbed Calcium Metabolism.—The calcium metabolism is also disturbed. MacCallum and Voegtlin showed that animals suffering from parathyroid tetany have an increased output of calcium salts in the urine and feces and a reduced amount of calcium in the blood and the brain. The intravenous injections of calcium salts into such animals leads to a prompt amelioration of the symptoms and life may be markedly prolonged by repeated injections. Apparently the parathyroid glands exert some influence upon the retention of calcium by the nerve tissues.

VARYING RESULTS OF MEDICINAL USE OF CALCIUM.—The suggestion that a lack of calcium may be the direct cause of the symptoms of tetany in man as well as in animals has led to its employment in human cases of tetany. The results have been conflicting; for while, in certain instances, marked improvement has apparently followed its use, in other cases, the results have been disappointing even where large doses were injected intravenously. Nevertheless, the possible relation of a disturbed calcium metabolism to various forms of human tetany is suggested by the fact that tetany occurs with unusual frequency in conditions that are associated with other alterations in the calcium metabolism, such as rickets, osteomalacia, pregnancy, etc.

Etiology of Tetany in Man

In certain districts tetany in man is endemic and occurs particularly in those following certain occupations (tailors and shoemakers). The cause of this type is quite unknown.

Tetany During Pregnancy and After Parturition.—The type of tetany that occurs during the later months of pregnancy as well as after parturition has been reproduced in animals; for after a partial excision of the parathyroid glandules an animal may remain free of tetany under ordinary circumstances but may develop the disease when pregnancy occurs. The partisans of the calcium theory point out that the losses of calcium from the mother during the growth of the fetus and during the secretion of milk may be responsible for the tetany in such cases.

Tetany in Infants.—Tetany and related conditions are particularly common in infants. Various changes in the parathyroid glands have been described in such patients, but no definite relation between these and the disease has been established. Since tetany occurs more especially in those who have been fed artificially, numerous attempts have been made to relate it to the diet. The calcium of cow's milk, for example, appears to be less easily absorbed than that of the mother's milk, so that such infants may possibly suffer from calcium want. Brown and Fletcher believe, however, that a retention of sodium chlorid, which, unlike calcium salts, increases nervous irritability, is responsible for the tetany of infants that have been fed artificially, especially on carbohydrate foods.

Gastric Tetany.—Tetany has also been observed in man in association with gastric disease, and particularly in patients who have long suffered from obstruction at the pyloric orifice. Whether this type is due to the absorption of some toxic substance from the stomach, or whether it is due to a loss of liquids, of salts, or of acid in consequence of the prolonged vomiting is not known. In such cases the parathyroid glands are usually intact and the condition is often relieved by gastro-enterostomy.

Relation to Parathyroid Insufficiency.—It is obvious, therefore, that tetany in man may occur under a variety of conditions and that its relation to parathyroid insufficiency is by no means proved, except in those rare cases that have followed operative excision of these glands. A residue of one-fourth or less of the total parathyroid tissue will protect operated animals from tetany, and there is no reason to believe from anatomical examinations that such a reduction, as a result of disease, is at all common in man. The relation of various clinical forms of tetany to that which follows excision of the parathyroid glands is, therefore, problematical. It is possible that in these patients there is a marked parathyroid insufficiency with no evident anatomical change, it is possible that the immediate cause of the tetany, such, for example, as a lack of calcium, may be produced not only by parathyroid deficiency but by other causes, or it is possible, finally, that no relation exists between the various clinical forms of the disease. Of these things we know almost nothing.

Parathyroid Medication

The administration of parathyroid substance by mouth has at times appeared to benefit patients suffering from the effects of parathyroidectomy, but the results obtained in animals after experimental excision have not been curative. The treatment of parathyroid deficiency by the administration of parathyroid substance is, therefore, less successful than the corresponding treatment of thyroid deficiency; but more successful, apparently, than the treatment of depancreatized animals with pancreatic tissue. In forms of tetany other than that caused by excision

of the parathyroids, the therapeutic results of parathyroid medication have been, on the whole, disappointing.

Transplantation.—The transplantation of parathyroid tissue from its normal site to other parts of the body has been successfully accomplished, and in the absence of other parathyroid tissue in the body (parathyroid want), this transplanted tissue may survive, functionate and prevent the development of tetany. The transplantation of these glandules from one animal to another is usually, if not always, unsuccessful, and there seems little encouragement for the hope that such surgical measures will permanently relieve a parathyroid deficiency.

The Thymus and the Status Lymphaticus

In man the weight of the thymus gland relative to the body weight is greatest at birth. Its absolute weight, however, increases up to about the time of puberty, after which it atrophies.

Effect of Thymus Excision

Complete extirpation of the thymus gland in young dogs apparently leads to serious disturbances in nutrition. After a latent period which may be followed by obesity, the animals show general weakness and cachexia, the growth of the long bones is retarded, the epiphyses become swollen, and the bones tend to bend (Klose and Vogt, Matti). These bony changes resemble those which occur in rickets. Pappenheimer failed to obtain similar changes in rats after thymectomy. To what extent such symptoms may occur in man is unknown. As a rule, the operative removal of the thymus from infants or children is incomplete, and nutritional disturbances after such an operation need not be feared.

Thymic Asthma and Thymic Death

The chief clinical interest in the thymus gland centers about the fact that sudden deaths, particularly in infants, are not infrequently accompanied by an enlargement of the thymus gland. The evidence at hand indicates that in many, and perhaps in all, cases the symptoms are due to the mechanical effect of the enlarged gland. Pressure upon the trachea has been demonstrated not only at autopsy, but during life by the x-ray, by tracheoscopy, and during intubation. During life dyspnea, either continuous or intermittent, accompanied by suffocative attacks and stridor, are the principal manifestations. These have been relieved by successful thymectomy. Pressure upon the blood vessels or upon the nerves that pass through the upper aperture of the thorax may also play a part in producing the symptoms associated with enlarged thymus.

Increased Lymphadenomatous Tissue.—In a certain number of sudden deaths, however, particularly in older persons, the thymus, though enlarged, does not seem to have been large enough to produce pressure symptoms. In such cases, and especially where there is a concomitant increase of lymphadenomatous tissue throughout the body, the view has been expressed that the unexpected death is due to some change in the constitution of the individual (status lymphaticus) or to some toxemia.

The Thymus in Graves' Disease

We have already pointed out that where partial thyroidectomy has failed to cure Graves' disease, further improvement may take place if a portion of the (often enlarged) thymus is extirpated or if the thymus gland be exposed to the destructive action of the x-ray. It is believed that certain of the symptoms observed in Graves' disease, and particularly the lymphocytosis and the cardiac disturbances, may depend upon a perverted function of the thymus. More investigation in this field is required, however, before our knowledge of the part played by the thymus is understood.

Status lymphaticus

Intimately associated with the occurrence of enlarged thymus is the enlargement of lymphatic tissue elsewhere in the body. Sudden deaths occurring in older children and adults, in which a mechanical pressure by the thymus appeared to be improbable, have been attributed by some to changes in the body accompanying this overgrowth of lymphatic tissue. The exact relations are uncertain, but in such cases there often appears to be a constitutional hypoplasia of the aorta and of the chromaffin tissues. Crowe and Wislocki observed such changes in the thymus and lymphatic apparatus after partial excision of the adrenals (see Adrenals).

The Pituitary Gland

The pituitary gland, or hypophysis cerebri, lies in the cavity of the sella turcica. It is composed of two distinct parts which differ in their structure, in their physiological activities, and in their development. The *anterior lobe* is composed of epithelial cells, many of which may show basophilic or eosinophilic granulations. It develops during embryonic life as an outpocketing of the epithelium which lines the vault of the buccopharyngeal pouch contiguous to the brain. The *posterior lobe* is composed mainly of glia cells and of nerve fibers. It arises from an outgrowth of the central nervous tissues.

In extra-uterine life the pituitary is separated by the sphenoid bone from the mucous membrane lining the nasal cavity; but occasionally, as

a result of developmental anomalies, the original connection may be retained, or cellular masses, similar in structure to the anterior lobe, may be found in the bone or in the vault of the pharynx. The posterior lobe, on the other hand, remains in connection with the brain by means of the infundibulum which pierces the fibrous covering of the sella, and a pocket from the third ventricular cavity extends down into the infundibulum.

Pars intermedia.—The anterior pituitary lobe lies over the posterior much as a catcher's mitt surrounds a baseball. When the two are separated the line of cleavage runs through a small cavity which appears to be a remnant of the original cavity formed by the outpocketing of the pharynx. During such a separation a number of epithelial cells which line the posterior part of this cavity are left in contact with the posterior lobe. These are known as the pars intermedia and to these cells have been attributed certain special physiological activities of the pituitary gland.

Action of Pituitary Extracts

In 1895 Oliver and Schäfer demonstrated that extracts from the pituitary gland cause a rise of blood pressure when injected intravenously. This rise is usually less marked but more prolonged than that produced by epinephrin. This active substance may be obtained from either the posterior lobe of the pituitary or from the pars intermedia. Possibly, as some have believed, it is formed in the latter and passes through the former on its way to the infundibular cavity.

On Smooth Muscle Tissues.—Pituitary extracts cause a rise of blood pressure through their constricting effects upon the blood vessels. They also lead to a contraction of other smooth muscle tissues in the body. Strips of uterine muscle, especially from a pregnant uterus, may be made to contract by the addition of pituitary extracts to solutions in which they are suspended. Pituitary extracts have been used during parturition for the treatment of uterine inertia. The muscular contractions of the stomach, intestines and bladder are likewise increased by pituitary extracts, and such extracts have been used successfully in certain cases of intestinal paresis after operation. The increased flow of milk after pituitary administration appears to be due to an increased contraction of the smooth muscle in the mammary gland rather than to an increased secretion. Finally, pituitary extracts increase the flow of urine. This is probably due in the main to an increased blood flow through the kidneys owing to a local dilatation of their vessels, but it is also possible that the renal cells are directly stimulated to increased activity.

Secretion of These Substances.—The relation of these various activities of pituitary extracts to normal or pathological vital processes is still unsettled. It is doubtful if they play any essential part in the regulation of the normal activities of smooth muscle, for animals from

which the posterior lobe of the pituitary gland has been removed exhibit no change in these activities. If, indeed, the substances present in pituitary extracts play a part in the normal activities of the body their loss is not felt, for the reason that the other substances can supply the deficiency. Only in diabetes insipidus is there reason to believe that an excess of pituitary extract may be responsible for the continuous and marked secretion of urine (see Diabetes insipidus).

Experimental Hypopituitarism

Complete removal of the pituitary gland is usually and probably always followed by death. According to Cushing, adult dogs die within two to five days after such an operation, while puppies may live from ten to thirty days or even longer. Among the symptoms manifested by such animals are tremors, fibrillary twitchings, slow respirations and pulse, fall of temperature, stupor and coma.

Effect of Partial Hypophysectomy.—Of particular interest are the results of partial hypophysectomy. A number of experimenters have shown that after partial removal of the gland from young animals there is a retardation of growth, a retardation or lack of sexual development and a tendency to obesity with reduced rate of metabolism (see Obesity).

Relation to Different Parts of Gland.—The relation of these various changes to the different portions of the pituitary gland has been a subject of frequent investigation and is not yet entirely settled. The anterior epithelial lobe appears to be the part that is indispensable for life, for, while its removal seems to be invariably fatal, animals have lived for months and more after complete removal of the posterior lobe. The lack of growth that follows partial hypophysectomy in young dogs is almost certainly due to a lack of anterior lobe secretion. The absence of sexual development and the metabolic disturbances are possibly due to removal of other parts of the gland, especially the pars intermedia.

Fröhlich's Syndrome and Related Conditions

Certain types of pituitary disease are associated with changes which resemble those that have been produced in dogs and other animals by partial removal of the pituitary gland. In the condition known as Fröhlich's syndrome (dystrophia adiposogenitalis), the individual has usually shown his first symptoms of pituitary disease in early life. In the fully developed condition there is a retardation of skeletal growth, sexual infantilism and obesity. The fat is distributed mainly about the abdomen, the buttocks, and the breasts, giving a feminine type of figure (Fig. 135). The extremities are short and the hands and feet are small. Sexual characteristics, primary as well as secondary, develop late

or imperfectly. The skin is dry. Variations from this typical picture are common. In adults there may be a regression of sex characteristics and obesity. Or again, in less typical cases, the obesity may be absent and the individual may present the appearance of an underdeveloped adolescent rather than that of a fat boy (Fig. 136).

Relation to Hypopituitarism.—That the typical syndrome of Fröhlich

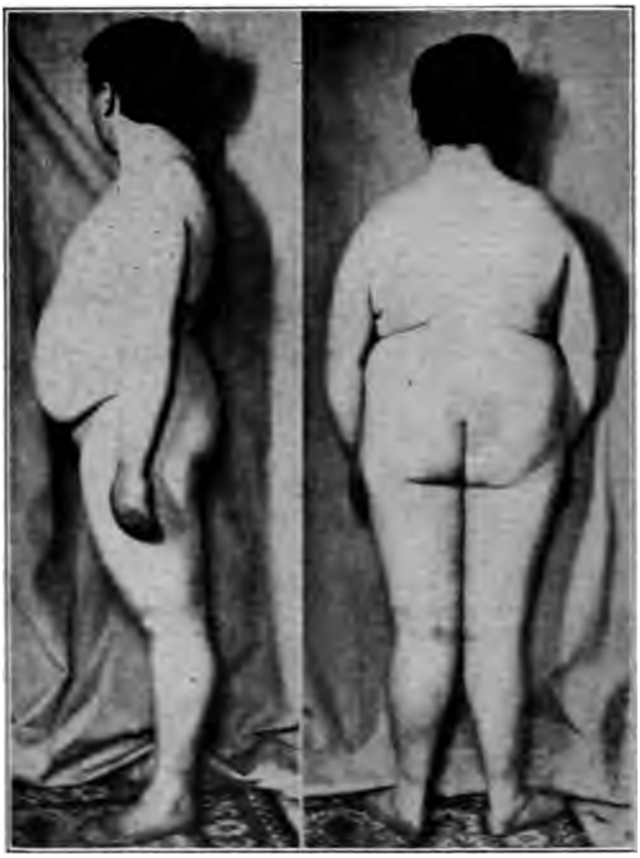


Fig. 135.—Fröhlich's Syndrome. History of Brain Tumor, Blindness Due to Primary [illegible] Atrophy, Retarded Growth, Sexual Infantilism, Obesity, and Diabetes Insipidus. Young Man 27 Years Old. Height 4 ft. 9½ in. (From Hewlett, Arch. Int. Med.

is due in the main to a hypofunction of the pituitary gland can hardly be doubted. The striking resemblance to the condition produced in animals by partial hypophysectomy is in itself suggestive. To this is added the fact that, in many cases, the pathological changes found in or about the pituitary gland are of such a character that one may easily infer compression or other damage to the gland. Finally, the general antithesis of this condition to the typical cases of acromegaly suggest

that they are due to glandular changes of an opposite type, and acromegaly, as we shall see, is probably due to hyperpituitarism.

The treatment of Fröhlich's syndrome and related conditions by means of pituitary substance has as yet led to no striking results. Unlike the use of thyroid preparations in myxedema, the administration of hypophysis substance does not compensate for a hypophysic deficiency. The conditions are comparable to those which are present in experimental pancreatic diabetes.

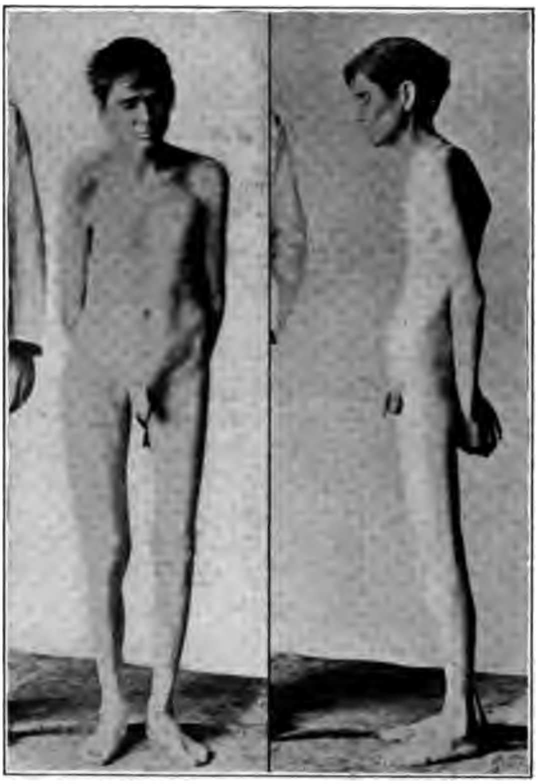


Fig. 136.—Pituitary Dystrophy in a Man 40 Years Old. Height 5 ft. 2 in. Note the Adolescent Figure, the Absence of Obesity, and the Absence of Hair on the Face and Pubic Region. (From Hewlett, Arch. Int. Med.)

Acromegaly

Acromegaly is believed to be due to an oversecretion of the pituitary gland, and particularly of its anterior lobe. It is characterized clinically by changes in the growth, the nutrition and the sexual characteristics. The hands and feet become enlarged, the nose is widened, the lips are thick, the lower jaw protrudes and in closing the mouth the lower incisors extend beyond the upper (Fig. 137). The voice becomes more hoarse and the skin more rough. The hair may fall or there may be an increase of hair in various parts of the body, such as occurs in the male. The sex organs are often enlarged but the sexual powers and in women the menses are often lost. Glycosuria is common (page 270).

Increase in Stature.—When a corresponding condition develops in growing individuals there is a marked increase in stature owing to an overgrowth of the long bones. Many giants are indeed sufferers from pituitary disease.

Overactivity of Anterior Lobe of Gland.—So far as the effects upon body growth and development are concerned, acromegaly and gigantism

are the opposite of Fröhlich's syndrome. The theory that the former are due to an overactivity of the pituitary gland, and particularly to an overactivity of its anterior lobe, is supported by anatomical examinations of the diseased gland, for these frequently show adenomatous tumors of the anterior lobe which might well give rise to an excessive secretion. Furthermore, partial excision of the diseased gland has caused a more or less complete regression of the changes in body form.

Other Types of Pituitary Disease

While, as we have just seen, acromegaly and Fröhlich's syndrome represent fairly definite complexes which may reasonably be attributed to hyperfunction or hypofunction, respectively, of the pituitary gland and more especially to such changes in its epithelial portion, a number of other patients suffering from pituitary disease display a mixture of symptoms, the interpretation of which in terms of hyperfunction or

a b c

Fig. 137.—Acromegaly. (a) Photograph Taken Before the Onset of the Disease, (b) and (c) at the Time of Examination. Note the Thickening of the Lips, the Protrusion of the Lower Jaw, and the Coarsening of the Features.

hypofunction is not simple. Thus obesity or emaciation have been associated with the changes in growth that characterize either acromegaly or Fröhlich's syndrome. Furthermore, the sexual functions, while always depressed in the typical Fröhlich's syndrome, may also be depressed in acromegaly.

Interpretation of Mixed Symptoms.—The exact interpretation of such mixed cases is often difficult. It seems probable, however, that many such atypical combinations are due to independent alterations in different portions of the hypophysis. If, as is generally admitted, the anterior lobe exercises a preponderating influence upon body growth and form, and if, as many believe, the posterior lobe or the pars intermedia

influence the body metabolism and the sex functions, then it is readily conceived that a hyperfunction in one part of the gland might be associated with a hypofunction in some other part, and that in this way a variety of mixed symptom groups might be produced. Even with such an assumption, however, the interpretation of pituitary complexes is often difficult, and the possibility of dysfunctions of certain parts of the gland must often be considered.

Fig. 138.—Obesity and Overgrowth Presumably Due to a Pituitary Dystrophy. Sixteen Years Old, Height 6 ft., Weight 185 lbs. Note the Absence of Axillary Hair, the Obesity, and the Long Legs with General Resemblance to a Feminine Type of Figure.

The Pineal Gland

Experimental Studies

The function of the pineal gland, or epiphysis cerebri, is but little understood. Extirpation is difficult and is succeeded by a high mortality of the animals operated upon. The recovery of a number of animals after complete excision, however, indicates that the gland is not essential for life. Many investigators have been unable to convince themselves that extirpation of the pineal body is followed by any characteristic change in growth, in sexual development or in metabolism (see, for example, Dandy). On the other hand, Foa as well as Sartesche has described premature sexual development after such operations on young animals and to this may be added premature somatic development and adiposity.

Effect of Pineal Substance on Animals.—Curiously enough, the administration of pineal substance to growing animals is said to lead to a group of symptoms that are, in a way, analogous to those described above as following extirpation of the gland. According to McCord, the oral or hypodermic administration of pineal substance derived from young animals to other young animals increased their rate of growth and brought about an early sexual maturity, but the animals thus treated did not become unusually large adults. The administration of pineal substance to adults produced no change.

Somatic Changes in Pineal Tumors

Tumors of the pineal gland are very rare and in the great majority of these no change in the somatic processes has been observed. In chil-

dren, and particularly in boys, however, the presence of a pineal tumor may be associated with the so-called pineal syndrome. The latter consists: (1) of early sexual maturity, with early development of the sex characteristics (voice, hair, and sex organs); (2) precocious mental development; (3) rapid growth, so that a child may have the stature of one much older; (4) obesity.

Possibly Due to Internal Hydrocephalus.—Here we see a group of symptoms which resemble those that have been described both after extirpation of the epiphysis in animals and following the feeding of its substance to young animals. It is, therefore, premature to speculate concerning the nature of the pineal change which could bring about such somatic alterations in development. Possibly, indeed, a portion of the changes included in the pineal complex, and particularly the obesity, are due not to the pineal directly but to the internal hydrocephalus which so frequently accompanies disease of this organ and which is known to influence the function of the pituitary gland.

The Adrenals

Like the pituitary, the adrenal glands are composed of two elements, which differ in their development, in their structure and in their physiological properties.

Adrenal Medulla.—The adrenal medulla consists mainly of nervous tissue which is closely related in development to the sympathetic nervous system. The medullary cells stain darkly with chromium salts and the adrenal medulla belongs, therefore, to the "chromaffin tissue system," which also includes various other collections of similar cells that lie in the neighborhood of the abdominal sympathetic ganglia. There is reason to believe that all these groups of chromaffin cells possess a common function, for they all yield on extraction blood pressure raising substances similar to epinephrin.

Adrenal Cortex.—The adrenal cortex is composed of columns of epithelial cells arranged for the most part in a radial manner. These develop from a mass of tissue which lies close to the kidney in the neighborhood whence the sex glands arise. Accessory masses of adrenal cortical tissue are at times found along the spermatic vein or about the pelvis of the kidney. The cortical cells of the adrenal are related to the luetin cells of the ovary and to the interstitial cells of the testis. The cortical cells contain relatively large quantities of cholesterin compounds.

Epinephrin

Like the posterior or nervous portion of the pituitary, the medulla or nervous portion of the adrenal gland contains a substance which causes

a marked rise of blood pressure when injected intravenously. This is known as epinephrin (adrenalin, suprarenin, etc.). Its chemical structure, which is now known (page 239), shows that it is related to the protein-building stone, tyrosin. It has been prepared synthetically.

Effects of Epinephrin Injection.—As Elliott pointed out, the physiological effects produced by the intravenous injection of epinephrin are the same as those which follow stimulation of the sympathetic nerve fibers. There is a marked constriction of the arteries and particularly of those which supply the abdominal viscera. Relatively little effect is produced upon the pulmonary arteries or upon those supplying the brain, while the coronary arteries of most laboratory animals (but not of man?) become dilated. The contractions of the pregnant uterus are also increased.

On the other hand, the injection of epinephrin, like sympathetic stimulation, tends to relax certain smooth muscle tissues. This happens, for example, in the smooth muscle surrounding the gastro-intestinal canal. Intestinal peristalsis is inhibited by epinephrin. Sympathetic stimulation tends, furthermore, to relax the muscles surrounding the bronchi, and epinephrin has been widely used for the treatment of bronchial asthma, a condition caused by spasm of this muscle (see Bronchial Asthma).

Finally, epinephrin injections, like stimulation of the sympathetic nerves, tends to convert the liver glycogen into glucose and thus to produce hyperglycemia and glycosuria (see Epinephrin Glycosuria).

Factors Controlling Epinephrin Secretion.—It is evident, therefore, that epinephrin produces a variety of important physiological effects when given in sufficiently large doses. The question may be asked, however, whether the amounts of epinephrin liberated from the adrenal glands is sufficient to produce these physiological effects under normal or pathological conditions, and if so what are the factors which control this liberation. Cannon and his associates have shown that the output of epinephrin from the adrenal glands is increased as a result of violent emotion, whether fear or anger. Pain and asphyxia also increase the output of epinephrin. During violent emotion certain changes occur in the functions of the body, among which are a cessation of gastro-intestinal movements, an increase of blood pressure, and glycosuria. In all probability, these may be attributed to this liberation of excessive amounts of epinephrin into the blood. Cannon has indeed pointed out, that the changes which follow such a liberation of epinephrin under condition of nervous strain may have been advantageous to the primitive man, in that they were of value in the fight for existence. The heightened blood pressure, the increased sugar in the blood, the bronchodilatation, and the reduction of fatigue, all of which result from the escape of epinephrin during emotional strain, might well be of immediate value in the combat

or in the flight that in primitive times was associated with the major emotions.

Action of Secretion in Quiet Life Unknown.—There is reason, therefore, for believing that under conditions of emotional stress a discharge of epinephrin into the blood takes place. Concerning the physiological action of the amounts that may escape into the blood under conditions of a quiet life, little is known. According to Hoskins, the epinephrin secretion during a reposeful life, if occurring at all, is below the threshold necessary to stimulate the sympathetic nervous system.

Excision of the Adrenals

When the adrenal glands are completely removed, death invariably follows. The blood pressure falls, the appetite is lost, symptoms of muscular weakness appear, and the animal finally develops increasing drowsiness and possibly convulsions and dies within one or several days. The symptoms which follow the total excision of the adrenal glands have often been attributed to a lack of epinephrin in the blood. There are many reasons, however, for believing that the fatal results of epinephrectomy are due, not to a lack of medullary substance and its secretion (epinephrin), but to a lack of the cortical portion of the glands. Thus the administration of epinephrin is of little or no value in preventing the consequences of experimental epinephrectomy. Biedl has shown, furthermore, that in certain species of fish where the cortical adrenal tissue is separated from the medullary tissue, the extirpation of the cortical organ (interrenal body) leads to death with typical symptoms of muscular weakness. Again, after recovery from partial epinephrectomy it is the cortical tissue which hypertrophies. Finally, if one regards the chromaffin tissue in other parts of the body as the functional equivalent of the adrenal medulla, it is difficult to understand the serious effect of removing only a part of the chromaffin tissue of the body. For all these reasons, therefore, it seems probable that the fatal effects following extirpation of the adrenal glands depend not upon a lack of medulla and of epinephrin but upon the absence of cortical tissue.

Addison's Disease

Certain of the characteristic manifestations of Addison's disease, and particularly the muscular weakness, the low blood pressure, the vomiting, and the diarrhea, are, in a general way, comparable to the symptoms produced by extirpation of the adrenal glands from animals. The further fact, that the majority of patients dying of Addison's disease show a bilateral destruction or atrophy of the adrenal glands, also favors the view that Addison's disease is due to an insufficiency of these glands. The administration of epinephrin has, as a rule, failed to stay the course of this disease; yet this is not surprising when we consider: (1) that it

also fails after experimental epinephrectomy; and (2) that the symptoms of adrenal deficiency probably depend mainly upon the lack of cortical rather than the lack of medullary tissue.

Characteristic Pigmentation.—The characteristic pigmentation of Addison's disease appears as a dark bronzing of the exposed and irritated parts of the skin, as well as of the skin about the genitalia, the nipples, axillae, etc. Pigmentation of the mucous membranes is remarkably frequent. The cause of this pigmentation is not definitely known. The coloring matter does not appear to be derived from the products of hemoglobin catabolism, but rather from certain of the building stones of the protein molecule (tyrosin, tryptophan, etc. See Melanin). Some of these substances are chemically related to epinephrin, and it seems probable that the pigmentation of Addison's disease depends upon some alteration in the epinephrin-forming function of the adrenal glands. Just what this alteration is, however, we do not know.

Hyperfunction of the Adrenals

We have seen that the major emotions are accompanied by a discharge of epinephrin from the adrenal glands and that this transient hyperfunction is probably responsible for certain of the bodily changes which accompany violent emotions. Concerning the possibility that a chronic increase of epinephrin in the blood may accompany certain pathological conditions and particularly chronic arterial hypertension, there has been much speculation. It is doubtful, however, if epinephrin is demonstrable in the circulating blood of normal individuals, and there is no evidence that the quantity is increased in conditions of chronic hypertension. Only in exophthalmic goiter have considerable increases of epinephrin in the circulating blood been reported, but, owing to the inaccuracies of the methods used, further work is required in order to establish this observation.

Effect of Adrenal Tumors.—Tumors of the adrenal glands do not as a rule cause any change in distant parts of the body. Occasionally, however, when such tumors have developed during childhood, there has been a marked acceleration of the body growth and a premature sexual development. At times, also, it has been noted that the development of adrenal tumors in women has led to a cessation of the menses and to an increased hairiness of the face and the linea alba. Thus it would seem that, in certain instances, tumors of the adrenal glands have influenced the growth and the sexual characteristics.

Internal Secretion of the Sex Glands

The sex glands not only form and liberate the specific reproductive cells (ova, spermatozoa) but they also exert a profound influence upon the development of the body and mind. That this influence depends upon chem-

ical rather than upon nervous influences was shown years ago by Berthold's experiment. Cockerels, whose testicles had been transplanted to some distant part of the body, developed the vocal powers, the combativeness, the comb and the sexual instincts of normal cocks.

Interstitial and Luetin Cells.—The influence of the sex glands upon development and upon temperament does not depend so much upon the reproductive cells proper as upon other cell groups in the sex organs. In the testes these are known as the interstitial cells of Leydig while in the ovaries they are the luetin cells. In a man, for example, the true sperm cells may degenerate, so that the individual becomes sterile; at the same time, however, the interstitial cells may remain functionally active so that the sex characteristics develop and are retained. Such a condition has been produced experimentally in animals by ligating the vasa deferentia or by exposing the testicles to the action of the x-ray. It occurs also in certain individuals suffering from undescended testes.

utein

Effect of Removal of Testicles.—When the testicles are entirely removed during early youth, so that not only the sperm but also the interstitial cells are lost, there is an almost complete failure in the development of the sexual characteristics. The skin remains smooth, the voice is high-pitched, fat develops about the buttocks, and the individual often attains an unusual height owing to an overgrowth of the long bones of the legs. This overgrowth is associated with a delayed union of the eriphyses. In addition, the dispositions of eunuchs differ from those of the average male. As a rule, they are less ambitious, less striving, more indolent, treacherous, and cowardly.

Influence of Sex Glands on Women.—The sexual glands produce a profound influence upon the body and mental functions of women. Cyclic changes in the blood pressure, the body temperature and the general nervous condition have been observed in connection with the menstrual function. The menopause, whether natural or artificial, is often associated with increased nervousness, skin flushings, and ultimately with increased weight. It is interesting in this connection that Hoskins found that when the ovaries had been removed from animals the vascular responses to certain test drugs were increased.

Interrelationship of the Internal Secretions

In reviewing the effects produced by changes in the internal secretions it is noteworthy that certain functions of the body appear to be particularly influenced by such chemical influences. We have seen, for example, that the *growth of the long bones* is increased in acromegaly and is diminished in Fröhlich's syndrome, that there is an increased length of the long bones in eunuchs, that the growth is overrapid in certain adrenal tumors and in certain disturbances of the pineal gland, and that

the growth is stunted in cretinism and in certain forms of experimental thymectomy.

Effect on Sexual Characteristics.—The internal secretions also exercise a profound effect upon the development of the sexual characteristics. Aside from the effects of the interstitial cells and the luetin cells, we may mention the sexual infantilism accompanying various forms of pituitary disease and cretinism, and the sexual precocity that is occasionally associated with pituitary, adrenal and pineal tumors.

On Body Metabolism.—Finally, the internal secretions influence the body metabolism. In certain disturbances obesity is common, as in pituitary disease, hypothyroidism, after castration, etc. Then, too, the effect of the various internal secretions upon the sugar mobilization and utilization in the body has been a subject of repeated studies, but the results of these studies are at the present time of a conflicting character.

Primary and Secondary Glandular Disturbances.—It is possible to interpret many of these manifestations either as the direct or as the indirect result of the primary glandular disturbance. In the case of the obesity associated with pituitary disease, for example, the collection of fat may be regarded as the direct result of the lack of pituitary secretion, or it may be due to a secondary thyroid or sex gland insufficiency.

Effect of Excision on Other Glands.—That the various glands of internal secretion do indeed affect each other is evident from the fact that excision of one gland has frequently been followed by secondary changes in other glands. After thyroidectomy, for example, the anterior lobe of the hypophysis increases in size. A variety of similar alterations have been noted; such as, swelling of the thyroid during menstruation and during pregnancy, enlargement of the adrenals during experimental hyperthyroidism, increase of lymphatic tissue during experimental hypofunction of the adrenals, the effect of various glands upon sexual development, etc.

Schemata of Relationships.—It is evident, therefore, that the internal secretions may not only neutralize or supplement one another, but that changes in one gland tend to alter the structure and presumably the secretion of other glands. Various efforts have been made to express these complex relationships in a schematic way, but at the present time the attempts to formulate the interrelationships, that doubtlessly exist between the various glands of internal secretion, suffer from a lack of facts. Until this deficiency is supplied, such schemata can be no more than working hypotheses which will doubtlessly be modified as more is learned of the relations existing between the internal secretions.

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A. Franklin	Feb 7 1923
F.R. McCrea	Feb 3
E. McHall	Feb 20
F.R. McCrea	Apr. 16.
R. Hethercuff	Apr. 7 1923
R. Hethercuff	May 9 1923
M. Lawson	May 2
M Hewitt	
R. Bulman	
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C. J. Bun[illegible]	